PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07C 311/37, A61K 31/41
A61K 31/18, 31/42, 31/425
C07C 311/46, C07D 263/58
C07D 277/74

A1

(11) International Publication Number: WO 93/15047

(43) International Publication Date: 5 August 1993 (05.08.93)

(21) International Application Number: PCT/GB93/00167

(22) International Filing Date: 27 January 1993 (27.01.93)

(30) Priority data:
9201755.7 28 January 1992 (28.01.92) GB

(71) Applicant *(for all designated States except US)*: BRITISH BIO-TECHNOLOGY LIMITED [GB/GB]; Watlington Road, Cowley, Oxford OX4 5LY (GB).

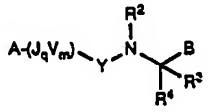
(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : BOWLES, Stephen, Arthur [GB/GB]; MILLER, Andrew [GB/GB]; WHITTAKER, Mark [GB/GB]; British Bio-technology Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB).

(74) Agent: WALLS, Alan, J.; British Bio-technology Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB).

(81) Designated States: AU, CA, FI, JP, KR, NO, NZ, PT, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: AMINO ACID DERIVATIVES AS PAF ANTAGONISTS



(I)

(57) Abstract

Compounds of general formula (I), wherein: A represents: a) a group -Q-X wherein Q represents an -O-, -S- or -NR- group (wherein R is as defined below) or a bond; and X represents a 5- or 6-membered aromatic or heterocyclic ring, b) a group -CN, $-NO_2$, $-N_3$ $-NRR^1$, -OR, $-C(=O)NHCHRR^1$, $-C(=O)NRR^1$, $-NRC(=O)R^1$, $-NRC(=O)OR^1$, $-S(=O)_2NHCHRR^1$, $-S(=O)_2NRR^1$, -COR, $-CO_2R$, $-SO_2R$, -SOR, -COX, $-SO_2X$, wherein X is as defined above, or a halogen atom; J represents a divalent alkanediyl, alkenediyl or alkynediyl group from 1 to 8 carbon atoms; q is 0 or 1; V represents a phenylene, furandiyl, tetrahydrofurandiyl, thiophenediyl, tetrahydothiophenediyl, thiazolediyl or tetrahydothiazolediyl group; m is 0 or 1; Y represents a bond, a $-CH_2-$, $-C(=O)-$, $-C(=S)-$, $-S(=O)_2-$ or $-P(=O)(OC_1-C_6$ alkyl)- group; R^2 represents hydrogen, $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-COC_1-C_6$ alkyl, $-CO_2C_1-C_6$ alkyl, $-CO_2(C_1-C_6$ alkyl)phenyl, $-(C_1-C_6$ alkyl)$CO_2C_1-C_6$ alkyl, $-(C_1-C_6$ alkyl)phenyl, $-C_3-C_8$ cycloalkyl, $-C_4-C_8$ cycloalkenyl or a group -D wherein D is as defined above; or R^2 together with R^3 and the atoms to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring; each of R^3 and R^4 may independently represent hydrogen, halogen, $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-(C_1-C_6$ alkyl)$CO_2C_1-C_6$ alkyl, $-(C_1-C_6$ alkyl)SC_1-C_6 alkyl, $-(C_1-C_6$ alkyl)OC_1-C_6 alkyl, $-(C_1-C_6$ alkyl)$N(C_1-C_6$ alkyl)$_2$, $-C_3-C_8$ cycloalkyl, $-C_4-C_8$ cycloalkenyl, $-(C_1-C_6$ alkyl)C_3-C_8 cycloalkyl, $-(C_1-C_6$ alkyl)C_4-C_8 cycloalkenyl, $-(C_1-C_6$ alkyl)OC_3-C_8 cycloalkyl, $-(C_1-C_6$ alkyl)OC_4-C_8 cycloalkenyl, $-(C_1-C_6$ alkyl)SC_3-C_8 cycloalkyl or $-(C_1-C_6$ alkyl)SC_4-C_8 cycl alkenyl, a side chain f a naturally occurring amino acid, a group -D as defined above or a $-(C_1-C_6$ alkyl)OD group wherein D is as defined above; or R^3 and R^4 together with the carbon atom to which they are attached form a C_3-C_8 cycloalkyl ring; B represents: a) a ZR^8 group wherein Z is a b nd, $-C(=O)-$, $-C(=O)O-$, $-CH_2O-$, $-CH_2OC(=O)-$, $-C(=S)-$, $-C(=S)O-$, $-CH_2S-$, $-CH_2OC(=O)NH-$, $-C(=O)NHSO_2-$ or $-SO_2NHC(=O)-$; b) a $-CH_2NR^9R^{10}$ group or a $-CONR^9R^{10}$ group; c) a group E where E is a 5- or 6-membered heterocyclic ring; or d) a group $-CH_2E$, $-C(=O)NHE$ or $-C(=O)NHCH_2E$, wherein E is as defined above; and their pharmaceutically and veterinarily acceptable acid addition salts and hydrates are antagonists of platelet activating factor (PAF) and as such are useful in the treatment or amelioration of vari us diseases or disorders mediated by PAF.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SK	Slovak Republic
CI	Côte d'Ivoire	KZ	Kazakhstan	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
CS	Czechoslovakia	LK	Sri Lanka	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	UA	Ukraine
DK	Denmark	MG	Madagascar	US	United States of America
ES	Spain	ML	Mali	VN	Viet Nam
FI	Finland	MN	Mongolia		

AMINO ACID DERIVATIVES AS PAF ANTAGONISTS

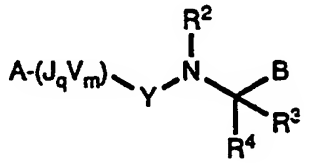
This invention relates primarily to novel substituted amino acid derivatives which possess pharmaceutical activity as antagonists of PAF.

Platelet activating factor (PAF) is a bioactive phospholipid which has been identified as 1-*O*-hexadecyl/octadecyl-2-acetyl-*sn*-glyceryl-3-phosphoryl choline. PAF is released directly from cell membranes and mediates a range of potent and specific effects on target cells resulting in a variety of physiological responses which include hypotension, thrombocytopenia, bronchoconstriction, circulatory shock, and increased vascular permeability (oedema/erythema). It is known that these physiological effects occur in many inflammatory and allergic diseases and PAF has been found to be involved in a number of such disorders including asthma, endotoxin shock, adult respiratory distress syndrome, glomerulonephritis, immune regulation, transplant rejection, gastric ulceration, psoriasis, and cerebral, myocardial and renal ischemia. Thus the compounds of the invention, by virtue of their ability to antagonise the actions of PAF, should be of value in the treatment of any of the above conditions and any other conditions in which PAF is implicated (e.g. embryo implantation).

Compounds that have been disclosed as possessing activity as PAF antagonists include compounds which are structurally related to the PAF molecule such as glycerol derivatives (EP-A-0238202), and heterocyclic compounds such as 5-oxy derivatives of tetrahydrofuran (US-4,888,337) and 2,5-diaryl tetrahydrofurans (EP-A-0144804). Recently a more potent 2,5-diaryl tetrahydrofuran derivative, (*trans*)-2-(3-methoxy-5-methylsulphonyl-4-propoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (L-659,989) has been disclosed (EP-A-0199324). In our International patent application no. WO 91/17157 we disclose a series of γ-butyrolactol derivatives as PAF antagonists. The compounds of WO 91/17157 differ from the 5-oxy derivatives of tetrahydofuran described in US-4,888,337 and from the 2,5-diaryl tetrahydrofurans such as L-659,989, in that they feature an appended heterocycle with an unsubstituted sp^2 nitrogen atom. There are a number of other PAF antagonists, in addition to those of WO 91/17157, for which the presence of a heterocyclic sp^2 nitrogen atom appears to be an important requirement for activity (Whittaker, M., Curr. Opin. Thera. Patents 2(5), 583-623 (1992)).

For the compounds of the present invention the presence of a heterocyclic group possessing an unsubstituted sp^2 nitrogen atom is not a strict requirement for PAF antagonist activity. The compounds of the present invention differ from the other PAF antagonists refered to above in that they are amino acid derivatives.

According to a first aspect of the invention there is provided a compound of general formula I:



I

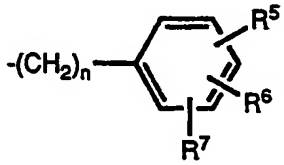
wherein:

A represents:

a) a group -Q-X wherein Q represents an -O-, -S- or -NR- group (wherein R is as defined below) or a bond; and

X represents a 5- or 6-membered aromatic or heterocyclic ring, which may optionally be fused to a benzene ring or to a further 5- or 6-membered aromatic or heterocyclic ring and wherein any of the rings may be optionally substituted with one or more substituents; and

optional substituents of the rings of the group X are -CN, $-NO_2$, halogen, $-C_1$-C_4 perfluoroalkyl, hydroxyl, carbonyl, thiocarbonyl, carboxyl, $-CONH_2$, a group -D wherein D is as defined below, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-NHR^{11}$, $-NR^{11}R^{11}$, CO_2R^{11} or $-CONHR^{11}$ wherein R^{11} is $-C_1$-C_6 alkyl, $-C_2$-C_6 alkenyl, $-C_2$-C_6 alkynyl, $-C_3$-C_8 cycloalkyl or $-C_4$-C_8 cycloalkenyl each of which is optionally substituted with one or more substituents selected from halogen, hydroxyl, amino, carboxyl, $-C_1$-C_4 perfluoroalkyl, $-C_1$-C_6 alkyl, $-C_2$-C_6 alkenyl, $-C_2$-C_6 alkynyl, $-C_3$-C_8 cycloalkyl, $-C_4$-C_8 cycloalkenyl, $-OC_1$-C_6 alkyl, $-SC_1$-C_6 alkyl, tetrazol-5-yl, a heteroaryl or heteroarylmethyl group or a group -D



wherein n is an integer from 0 to 3, and each of R^5, R^6 and R^7 is independently hydrogen, -C_1-C_6 alkyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -N(C_1-C_6 alkyl)$_2$, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -OCH_2Ph, halogen, -CN, -CF_3, -CO_2H, -CO_2C_1-C_6 alkyl, -$CONH_2$, -$CONHC_1$-C_6 alkyl, -CON(C_1-C_6 alkyl)$_2$, -CHO, -CH_2OH, -NH_2, -$NHCOC_1$-C_6 alkyl, -SOC_1-C_6 alkyl, or -SO_2C_1-C_6 alkyl; or

b) a group -CN, -NO_2, -N_3 -NRR^1, -OR, -C(=O)$NHCHRR^1$, -C(=O)NRR^1, -$NRC(=O)R^1$, -$NRC(=O)OR^1$, -S(=O)$_2NHCHRR^1$, -S(=O)$_2NRR^1$, -COR, -CO_2R, -SO_2R, -SOR, -COX, -SO_2X, wherein X is as defined above, or a halogen atom;

each of R and R^1 independently represents a hydrogen atom, -C_1-C_{18} alkyl, -C_2-C_{18} alkenyl, -C(=O)C_1-C_8 alkyl, -C(=O)OC_1-C_8 alkyl, -C(=O)OC_2-C_8 alkenyl, a group -D as defined above, or -(C_1-C_8 alkyl)X wherein X is as defined above;

J represents a divalent alkanediyl, alkenediyl or alkynediyl group from 1 to 8 carbon atoms which may be a straight or branched-chain, wherein the said group is either unsubstituted or substituted by one or more substituents selected from hydroxy, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, halogen, -CF_3, and -CN;

q is 0 or 1;

V represents a phenylene, furandiyl, tetrahydrofurandiyl, thiophenediyl, tetrahydothiophenediyl, thiazolediyl or tetrahydothiazolediyl group, wherein the said group is either unsubstituted or substituted by one or more substituents selected from hydroxy, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, halogen, -CF_3, and -CN;

m is 0 or 1;

Y represents a bond, a -CH_2-, -C(=O)-, -C(=S)-, -S(=O)$_2$- or -P(=O)(OC_1-C_6 alkyl)- group provided that when Y is -S(=O)$_2$- the group Q is not a bond;

R^2 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -CO_2C_1-C_6 alkyl, -CO_2(C_1-C_6 alkyl)phenyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)phenyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or a group -D wherein D is as defined above;

or R^2 together with R^3 and the atoms to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

each of R^3 and R^4 may independenly represent hydrogen, halogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)$N(C_1$-C_6 alkyl)$_2$, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)OC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)OC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)SC_3-C_8 cycloalkyl or -(C_1-C_6 alkyl)SC_4-C_8 cycloalkenyl (any of which may optionally be substituted with one or more substituents selected from halogen, hydroxyl, nitro, nitrile or carboxyl), a side chain of a naturally occurring amino acid, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

or R^3 and R^4 together with the carbon atom to which they are attached form a C_3-C_8 cycloalkyl ring;

B represents:

a) a ZR^8 group wherein Z is a bond, -C(=O)-, -C(=O)O-, -CH_2O-, -CH_2OC(=O)-, -C(=S)-, -C(=S)O-, -CH_2S-, -CH_2OC(=O)NH-, -C(=O)NHSO_2- or -SO_2NHC(=O)- and;

R^8 is hydrogen, -C_1-C_{18} alkyl, -C_2-C_{18} alkenyl, -C_2-C_{18} alkynyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)OC_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or pyridyl, (any of which may optionally be substituted with one or more substituents selected from halogen, hydroxyl, nitro, nitrile or carboxyl), -C_1-C_4 perfluoroalkyl, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

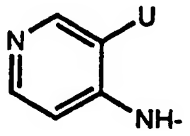
b) a -$CH_2NR^9R^{10}$ group or a -$CONR^9R^{10}$ group wherein each of R^9 and R^{10} is independently hydrogen, -C_1-C_{18} alkyl, -C_2-C_{18} alkenyl, -C_2-C_{18} alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or pyridyl (any of which may optionally be substituted with one or more substituents selected from halogen, hydroxyl, nitro, nitrile or carboxyl) or a group -D as defined above;

or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

c) a group E where E is a 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from nitrogen, oxygen and sulphur, which may optionally be fused to a benzene ring, and the ring may be optionally substituted with one or more substituents selected from -C_1-C_6 alkyl, -OC_1-C_6 alkoxy, halogen, -CF_3 and -CN; or

d) a group -CH_2E, -C(=O)NHE or -C(=O)NHCH_2E, wherein E is as defined above;

provided that when A is a group:



wherein U is -NO_2 or -NH_2 and J is a group -CHR- wherein R is as defined above; or

when A is OMe, -NHCOMe, -NO_2 or -CN, q is 0, Y is -SO_2- or -CO- and Z is other than a bond or a -C(=O)O- group; or

when A is -N_3, J is -CH_2- and Y is -SO_2-;

then V is not a 1,4-phenylene group; and

provided that when q is 0, m is 0 and Z is other than a bond or a -C(=O)O- group, then the grouping AY- is other than t-butyloxycarbonyl or benzyloxycarbonyl;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof;

Hereafter in this specification the term "compound" includes "salt" or "hydrate" unless the context requires otherwise.

As used herein the term "halogen" or its abbreviation "halo" means fluoro, chloro, bromo or iodo.

As used herein the term "C_1-C_6 alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to six carbon atoms. Illustrative of

such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl.

As used herein the term "C_1-C_8 alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to eight carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, heptyl and octyl.

As used herein the term "C_1-C_{18} alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to eighteen carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, decyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, and octadecyl. From one to six carbon atoms may be preferred.

As used herein the term "C_2-C_6 alkenyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "C_2-C_8 alkenyl" refers to straight chain or branched chain hydrocarbon groups having from two to eight carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2-butenyl, 2-methyl-2-propenyl, 3-pentenyl, 5-hexenyl, 6-heptenyl and 7-octenyl.

As used herein the term "C_2-C_{18} alkenyl" refers to straight chain or branched chain hydrocarbon groups having from two to eighteen carbon atoms and having in addition one or more double bonds, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2-butenyl, 2-methyl-2-propenyl, geranyl, and farnesyl. From two to six carbon atoms may be preferred.

As used herein the term "C_2-C_6 alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein the term "C_2-C_{18} alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to eighteen carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 10-undecynyl, 4-ethyl-1-octyn-3-yl, 7-dodecynyl, 9-dodecynyl, 10-dodecynyl, 3-methyl-1-dodecyn-3-yl, 2-tridecynyl, 11-tridecynyl, 3-tetradecynyl, 7-hexadecynyl and 3-octadecynyl. From two to six carbon atoms may be preferred.

As used herein, the term "C_1-C_4 perfluoroalkyl" refers to straight chain or branched chain groups having from one to four carbon atoms and substituted by more than one fluorine atom. This term would include for example, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoro-n-propyl, sexafluoro-i-propyl, septafluoro-n-propyl, septafluoro-i-propyl, 4,4,4-trifluoro-n-butyl, nonafluoro-n-butyl, nonafluoro-sec-butyl and nonafluoro-i-butyl.

As used herein the term "OC_1-C_6 alkyl" refers to straight chain or branched chain alkoxy groups having from one to six carbon atoms. Illustrative of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy and hexoxy.

As used herein the term "SC_1-C_6 alkyl" refers to straight chain or branched chain alkylthio groups having from one to six carbon atoms. Illustrative of such alkyl groups are methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, neopentylthio and hexylthio.

As used herein, the term "C_3-C_8 cycloalkyl" refers to an alicyclic group having from 3 to 8 carbon atoms. Illustrative of such cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, the term "C_4-C_8 cycloalkenyl" refers to an alicyclic group having from 4 to 8 carbon atoms and having in addition one or more double bonds. Illustrative of such cycloalkenyl groups are cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein, the term "5- or 6-membered heterocyclic ring" refers to such rings having from 5 to 6 atoms in the ring wherein the heteroatom(s) may be one or more nitrogen, oxygen or sulphur atoms. For example heterocycles containing nitrogen, oxygen, or sulphur alone or containing two nitrogen atoms, a nitrogen and an oxygen atom, a nitrogen and a sulphur atom, two nitrogen atoms and an oxygen atom, two nitrogen atoms and a sulphur atom, three nitrogen atoms or four nitrogen atoms.

As used herein, the term "nitrogen-containing heterocyclic ring" refers to an aromatic or alicyclic ring comprising one or more nitrogen atoms and optionally one or more other heteroatoms. Illustrative of such rings are pyrrolidine, piperidine, hexamethyleneimine, heptamethylenimine, morpholine and piperazine.

As used herein, the term "side chain of a naturally occurring amino acid" includes the side chains of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, glycine, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, α–aminoadipic acid, α–amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, α–methylserine, ornithine, pipecolic acid, and thyroxine. The amino acid side chains may be protected; for example the carboxyl groups of aspartic acid, glutamic acid and α–aminoadipic acid may be esterified (for example as a C_1-C_6 alkyl ester), the amino groups of lysine, ornithine, 5-hydroxylysine, 4-hydroxyproline may be converted to amides (for example as a COC_1-C_6 alkyl amide) or carbamates (for example as a $C(=O)OC_1$-C_6 alkyl or $C(=O)OCH_2Ph$ carbamate), the hydroxyl groups of 5-hydroxylysine, 4-hydroxyproline, serine, threonine, tyrosine, 3,4-dihydroxyphenylalanine, homoserine, α–methylserine and thyroxine may be converted to ethers (for example a C_1-C_6 alkyl or a (C_1-C_6 alkyl)phenyl ether) or esters (for example a $C(=O)C_1$-C_6 alkyl ester) and the thiol group of cysteine may be converted to thioethers (for example a C_1-C_6 alkyl thioether) or thioesters (for example a $C(=O)C_1$-C_6 alkyl thioester). The stereochemistry at the carbon atom to which the amino acid side chain is attached may be either D or L.

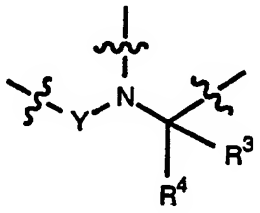
In compounds of this invention, the presence of several asymmetric carbon atoms gives rise to diastereoisomers, each of which consists of two enantiomers, with the appropriate R or S stereochemistry at each chiral center. The invention

is understood to include all such diastereoisomers, their optically active enantiomers and mixtures thereof.

The term "pharmaceutically or veterinarily acceptable acid addition salt" refers to a salt prepared by contacting a compound of formula (I) with an acid whose anion is generally considered suitable for human or animal consumption.

Examples of pharmaceutically and/or veterinarily acceptable acid addition salts include the hydrochloride, sulphate, phosphate, acetate, propionate, lactate, maleate, succinate and tartrate salts.

It is considered that the main structural feature of compounds of general formula I that is particularly significant in providing their PAF antagonist activity, is the subunit (i)



(i)

The linkage -(J_qV_m)- is considered to function as a spacer element, separating the the amino acid subunit from the group A. The nature or identity of the linkeage -(J_qV_m)- is therefore not thought to be particularly critical and any of the wide range of -(J_qV_m)- groupings specified above may be used with retention of PAF antagonist activity. Likewise, since the presence of the subunit (i) appears to be crucial for retention of PAF antagonist activity, there may be considerable variation of the substituent groups R^2, and B without loss of such activity. Any of the the wide range of substituents R^2 and B defined above may be used with retention of PAF antagonist activity. The group A also appears to be important for activity. There may be considerable variation of the nature of group A without loss of activity. Any of the wide range of heterocycles and/or functional groups that contain heteroatoms defined above for A may be used with retention of PAF antagonist activity.

Preferred compounds include those in which, independently or in any compatible combination:

A represents a group -Q-X in which

X represents a pyridyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indolyl, quinolinyl, triazolyl, phenyl, furanyl, thiazolyl, thiadiazolyl or a oxadiazolyl group, all these groups being optionally substituted as defined for general formula I (typical examples of X are 3-nitropyrid-4-yl, 3-N-acetylpyrid-4-yl, benzo[b]thien-2-yl, benzimidazol-2-yl, benzoxazol-2-yl, benzthiazol-2-yl, 5-chlorobenzoxazol-2-yl, indol-3-yl, 2-methylquinolin-4-yl, 4-methyl-5-(2-thienyl)-1,2,4-triazol-3-yl, 4-methyl-5-methylthio-1,2,4-triazol-3-yl, phenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, N-acetyl-4-aminophenyl, furan-2-yl, 4,5-dihydrothiazol-2-yl, 1,2,3-thiadiazol-4-yl, 5-(2-pyridyl)-1,3,4-oxadiazol-2-yl); or

A represents a -CN, $-NO_2$, $-N_3$, $-NRR^1$, -OR, $-C(=O)NHCHRR^1$, $-S(=O)_2NHCHRR^1$, -COR, $-CO_2R$, $-NRC(=O)R^1$, $-NRC(=O)OR^1$, -COX or $-SO_2X$ group;

R represents a hydrogen atom, a $-C_1$-C_{18} alkyl (for example ethyl, n-butyl, i-butyl, t-butyl or heptyl) group, a $-C(=O)C_1$-C_8 alkyl (for example acetyl) group, a group -D, or a $-(C_1$-C_8 alkyl)X group;

R^1 represents a hydrogen atom, a $-C_1$-C_{18} alkyl (for example methyl, t-butyl, pentyl or heptadecyl) group, a phenyl group, or a $-C(=O)OC_1$-C_8 alkyl (for example $-CO_2Et$) group;

J (if present) represents a $-C_1$-C_8 alkanediyl (for example methylene, propylene or pentylene) group;

V (if present) represents a phenylene group, particularly a 1,3- or a 1,4-phenylene group optionally substituted by halogen (for example fluorine) atom or a $-OC_1$-C_6 alkyl (for example ethoxy) group, or a thiophenediyl (for example a 2,5-thiophenediyl) group;

Y represents a bond, a $-CH_2-$, $-C(=O)-$ or $-S(=O)_2-$ group;

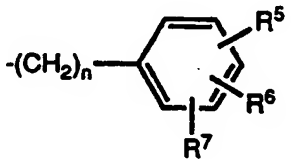
R^2 represents a hydrogen atom, a $-C_1$-C_6 alkyl (for example methyl) group, a group -D or, together with R^3 and the atoms to which they are attached, forms a 5 to 8 membered nitrogen-containing heterocyclic (for example morpholino) ring;

R^3 represents a hydrogen atom, a $-C_1$-C_6 alkyl group, a $-(C_1$-C_6 alkyl)CO_2C_1-C_6 alkyl (for example $-CH_2CO_2Et$) group, the side chain of a

naturally occurring amino acid (for example the side chain of leucine or isoleucine), a group -D or R^3, together with R^2 and the atoms to which they are attached, forms a 5 to 8 membered nitrogen-containing heterocyclic ring (for example a morpholino ring) or together with R^4 and the carbon atom to which they are attached forms a C_3-C_8 cycloalkyl (for example cyclohexyl) ring;

R^4 represents a hydrogen atom, a group -D or together with R^3 and the carbon atom to which they are attached forms a C_3-C_8 cycloalkyl (for example cyclohexyl) ring;

D represents a



group wherein;

n represents an integer of 0, 1 or 3;

R^5 represents a hydrogen atom;

R^6 represents a hydrogen atom;

R^7 represents a hydrogen atom;

B represents a ZR^8 group, a group E, a -CH_2E group or a -(C=O)NHCH_2E group;

Z represents a bond, a -C(=O)O- group, a -CH_2O- group or a -CH_2OC(=O)- group;

R^8 represents hydrogen atom, a -C_1-C_{18} alkyl (for example methyl, ethyl or undecyl) group, a -C_2-C_{18} alkenyl (for example allyl) group or a -(C_1-C_6 alkyl)OC_1-C_6 alkyl (for example 2-methoxyethyl) group;

E represents a tetrahydrofuranyl (for example 2-tetrahydrofuranyl) group, an indolyl (for example 3-indolyl) group or a tetrazolyl group;

Particularly preferred compounds include:

1. N-4-Azidomethylphenylsulphonyl-L-leucine ethyl ester,

2. N-Methyl-N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester,
3. N-Methyl-N-4-(N'-3-nitropyrid-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
4. N-4-(4-Methyl-5-(2-thienyl)-1,2,4-triazol-3-yl)thiomethylphenyl-sulphonyl-L-leucine ethyl ester,
5. N-4-(N'-3,4-Dimethoxyphenyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
6. N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucine ethyl ester,
7. N-Methyl-N-4-(N'-3,4-dimethoxyphenyl)aminomethylphenylsulphonyl-3-aminopropionic acid ethyl ester,
8. N-Methyl-N-4-(N'-(3,4-dimethoxyphenyl)-N'-acetyl)aminomethylphenyl-sulphonyl-3-aminopropionic acid ethyl ester,
9. N-4-(Benzthiazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl methyl ether,
10. N-4-Azidomethylphenylsulphonyl-L-leucine ethyl ether,
11. N-Methyl-N-4-azidomethylphenylsulphonyl-L-leucine ethyl ether,
12. N-Methyl-N-4-(N'-3-nitropyrid-4-yl)aminomethylphenylsulphonyl-L-leucinyl ethyl ether,
13. N-4-(Benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl ethyl ether,
14. N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl ethyl ether,
15. N-Methyl-N-4-(4-methyl-5-methylthio-1,2,4-triazol-3-yl)thiomethyl-phenylsulphonyl-L-leucinyl ethyl ether,
16. N-4-(5-(2-Pyridyl)-1,3,4-oxadiazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl ethyl ether,
17. N-Methyl-N-4-(N'-benzthiazol-2-yl)aminomethylphenylsulphonyl-L-leucinyl ethyl ether,
18. N-4-(Benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl methoxyethyl ether,
19. N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylcarbonyl-L-leucinyl ethyl ether,
20. N-Benzyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-2-phenylethylamine,
21. N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-1,2-diphenylethylamine,
22. N-Methyl-N-4-(5-chlorobenzoxazol-2-yl)thiomethylphenylsulphonyl-1,2-diphenylethylamine,
23. N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylcarbonyl-cyclohexylamine,

24. N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-cyclohexylamine,
25. N-3-(Benzoxazol-2-yl)thiopropylsulphonylmorpholine,
26. N-4-(4,5-Dihydrothiazol-2-yl)thiomethylphenylsulphonyl-L-leucine ethyl ester,
27. N-4-(N'-Benzimidazol-2-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
28. N-4-(N'-3-Phenylpropyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
29. N-4-(N'-Heptyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
30. N-Methyl-N-6-(benzoxazol-2-yl)thiohexanoyl-L-leucine ethyl ester,
31. N-Methyl-N-4-(N'-hexanoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
32. N-Methyl-N-4-(N'-hexadecanoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
33. N-Methyl-N-4-(N'-4-methoxybenzoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
34. N-Methyl-N-4-(N'-3,5-dimethoxybenzoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
35. N-Methyl-N-4-(N'-furan-2-ylcarbonyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
36. N-Methyl-N-4-(N'-acetyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
37. N-Methyl-N-4-(N'-t-butyloxycarbonyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
38. N-4-(N'-Acetyl)amino-3-fluorophenylsulphonyl-L-leucine ethyl ester,
39. N-4-(N'-Acetyl)aminophenylsulphonyl-L-isoleucine allyl ester,
40. N-4-Cyanophenylsulphonyl-L-leucine ethyl ester,
41. N-4-Nitrophenylsulphonyl-L-leucine ethyl ester,
42. N-4-(N'-Acetyl)aminophenylsulphonyl-L-leucinyl ethyl ether,
43. N-4-(N'-Acetyl)aminophenylsulphonyl-L-leucinol,
44. N-4-(N'-Acetyl)aminophenylsulphonyl-L-leucine,
45. N-Methyl 4-(N'-Acetyl)aminophenylsulphonamide,
46. N-Dodecyl 4-(N'-Acetyl)aminophenylsulphonamide,
47. N-4-n-Butoxyphenylcarbonyl-L-leucine ethyl ester,
48. N-3,4,5-Triethoxyphenylcarbonyl-L-leucine ethyl ester,
49. N-4-Phenylbutanoyl-L-leucine ethyl ester,
50. 1,3-Di(N-sulphonyl-L-leucine ethyl ester)benzene,
51. N-3-(O-Ethyl-L-leucinecarboxy)phenylsulphonyl-L-leucine ethyl ester,

52. N-4-(Hydroxycarbonyl)phenylsulphonyl-L-leucine ethyl ester,
53. N-4-(N'-Acetyl)aminophenylsulphonylglycine ethyl ester,
54. N-4-(N'-Acetyl)aminophenylsulphonyl-L-phenylalanine ethyl ester,
55. N-4-(N'-Acetyl)aminophenylsulphonyltetrahydrofurfurylamine,
56. N-4-(N'-Acetyl)aminophenylsulphonyltryptamine,
57. 5-(Phenylsulphonyl)thien-2-ylsulphonyl-L-leucine ethyl ester,
58. N-Methyl-N-4-(N'-4-(N"-acetyl)aminophenylsulphonyl)aminomethyl-phenylsulphonyl-L-leucine ethyl ester,
59. N-Methyl-N-4-(N'-2-benzo[b]thienylcarbonyl)aminomethylphenyl-sulphonyl-L-leucine ethyl ester,
60. N-4-(N'-2-Indolol-3-ylethyl)aminomethylphenylsulphonyl-L-leucinyl ethyl ether,
61. N-Methyl-N-4-(2-methyl-4-quinolinoxy)methylphenylsulphonylcyclo-hexylamine,
62. N-Methyl-N-4-(2-methyl-4-quinolinoxy)methylphenylsulphonyl-L-leucine ethyl ester,
63. N-Benzyloxycarbonyl-L-leucine tetrahydrofurfurylamide,
64. N-Methyl-N-4-(N'-acetyl-N'-methyl)aminophenylsulphonylcyclohexyl-amine,
65. N-4-(N'-Acetyl)aminophenylsulphonyl-L-leucinyl acetate,
66. N-Methyl-N-4-(N'-t-butyloxycarbonyl)aminomethylphenylsulphonyl-L-leucine,
67. N-Methyl-N-4-(N'-2-benzo[b]thienylcarbonyl)aminomethylphenyl-sulphonyl-L-leucine,
68. N-4-(1,2,3-Thiadiazol-5-yl)phenylmethyl-L-leucine ethyl ester,
69. N-4-(1,2,3-Thiadiazol-5-yl)phenylmethyl-L-phenylalanine ethyl ester,
70. N-Methyl-N-4-(N'-3-N"-acetylaminopyrid-4-yl)aminomethylphenyl-sulphonyl-L-leucine ethyl ester,
71. N-t-Butyloxycarbonyl-L-leucine ethyl ester,
72. N-4-(2-Methyl-4-quinolinoxy)methylphenylsulphonyl-L-leucine ethyl ester.

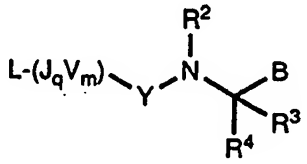
Compounds of general formula I may be prepared by any suitable method known in the art and/or by the following process, which itself forms part of the invention.

According to a second aspect of the invention, there is provided a process for preparing a compound of general formula I as defined above, the process comprising:

a) treating a compound represented by general formula II

AH II

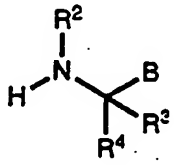
wherein A is as defined in general formula I, with a suitable base, followed by a compound of general formula III



III

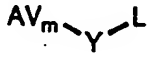
wherein R^2, R^3, R^4, J, q, V, m, Y and B are as defined in general formula I, and L is a leaving group such as chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy; or

b) for compounds of general formula I in which q is 0, treating a compound of general formula IV:



IV

wherein R^2, R^3, R^4, and B are as defined in general formula I with a suitable base, followed by a compound of general formula V:



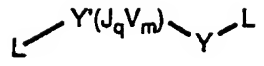
V

wherein A, V, m and Y are as defined in general formula I and L is a leaving group as defined above; or

c) for compounds of general formula I in which A is -C(=O)NHCHRR^1, -C(=O)NRR^1, -S(=O)2NHCHRR^1 or -S(=O)2NRR^1, treating a compound of general formula VI:

PH VI

wherein P is a group -NHCHRR^1 or -NRR^1 with a suitable base, followed by a compound of general formula VII:



VII

wherein J, q, V, m and Y are as defined in general formula I, L is a leaving group as defined above, Y' is a -C(=O)- or -SO_2- group and L' is a leaving group as defined for L; and

d) optionally after any one of steps (a) to (c), converting, in one or a plurality of steps, a compound of general formula I into another compound of general formula I.

The reaction of step (a) can, for preference, be conducted in an aprotic solvent (e.g. tetrahydrofuran, N,N-dimethylformamide or acetonitrile) to yield compounds of general formula I. Suitable bases include sodium hydride, potassium hydride, sodium bis(trimethylsilyl)amide or potassium hydroxide. In the case where an unsymmetrically substituted starting reagent is used the reactions can yield an isomeric mixture, which is separated by chromatography to yield compounds of general formula I.

The reaction of step (b) can, for preference, be conducted in an aprotic solvent (e.g. tetrahydrofuran, N,N-dimethylformamide or acetonitrile) to yield compounds of general formula I. Suitable bases include sodium hydride, potassium hydride or sodium bis(trimethylsilyl)amide when Y is a -CH_2- group and triethylamine when Q is other than a -CH_2- group.

The reaction of step (c) can, for preference, be conducted in an aprotic solvent (e.g. tetrahydrofuran, N,N-dimethylformamide or acetonitrile) to yield compounds of general formula I. A suitable base is triethylamine.

By means of step (d) compounds of general formula I wherein B is a -CO_2R^8 group can be converted to compounds of general formula I in which B is a -CO_2H group by acid or base catalysed hydrolysis in a protic solvent. Suitable acids for use in the hydrolysis include sulphuric and hydrochloric acids whilst base hydrolysis can be catalysed with sodium or potassium hydroxide.

If B represents a -CO_2R^8 group in which R^8 is a benzyl group, the conversion of B from an ester to an acid can also be effected by hydrogenation in a suitable solvent, for example, a lower alcohol such as ethanol using a noble metal catalyst such as palladium or platinum.

Also by means of step (d), compounds of general formula I in which B is a $-CO_2R^8$ group can be converted to compounds of general formula I in which B represents a $-CH_2OH$ group by reduction using any suitable method although lithium aluminium hydride or diisobutyl aluminium hydride in an aprotic solvent such as diethyl ether or toluene have proved to be particularly appropriate.

In a further variation of step (d), compounds of general formula I in which A is a group Q-X in which Q is an -NR- group or in which A is a group $-NRR^1$, $-NRC(=O)R^1$ or $-NRC(=O)OR^1$ wherein R^1 is as defined in general formula I and R is hydrogen can be converted to similar compounds of general formula I in which R is other than hydrogen by reaction with a suitable base (e.g. sodium hydride, potassium hydride, sodium bis(trimethylsilyl)amide, or potassium hydroxide), followed by a compound of general formula VIII

RL VIII

wherein R is as defined in general formula I and L is a leaving group as defined above.

Also by means of step (d) compounds of general formula I wherein A is Q-X and Q is an -NR- group, maybe prepared by treating a compound of general formula I wherein A is a $-NRR^1$ group wherein R^1 is as defined in general formula I and R is a hydrogen atom, with a suitable base (e.g. sodium hydride, potassium hydride, sodium bis(trimethylsilyl)amide, or potassium hydroxide), followed by a compound of general formula IX

XL IX

wherein X is as defined in general formula I and L is a leaving group as defined above;

Also by means of step (d) compounds of general formula I wherein A is a group $-NRR^1$ wherein R and R^1 are hydrogen, maybe prepared by reduction of a compound of general formula I wherein A is a group $-N_3$. Appropriate reduction methods are hydrogenation over a noble metal catalyst such as palladium or platinum in a solvent such as a lower alcohol or treatment with triphenylphosphine in wet tetrahydrofuran.

Derivatives of general formulae II, III, IV, V, VI, VII, VIII and IX are generally available or may be prepared by a number of methods known to those skilled in the art.

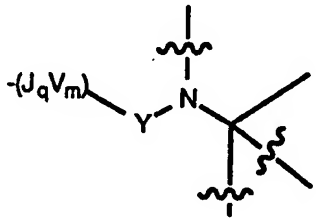
The appropriate solvents employed in the above reactions are solvents wherein the reactants are soluble but do not react with the reactants. The preferred solvents vary from reaction to reaction and are readily ascertained by one of ordinary skill in the art.

By analogy with the compounds disclosed in our earlier application (No. PCT/GB 93/00010) it is expected that certain of the compounds of general formula I claimed herein may have significant activity as angiotensin II antagonists. Angiotensin II is a bioactive octapeptide which is formed from angiotensin I by the action of angiotensin converting-enzyme. Angiotensin II is a powerful vasopressor agent which has been implicated as a causative agent of high blood pressure in various mammalian species, such as the rat, dog and man. Angiotensin II elevates blood pressure *via* binding to specific angiotensin II receptors on cell membranes. Thus the compounds of the invention, by virtue of their ability to antagonise the actions of angiotensin II, should be of value in the treatment of elevated blood pressure and congestive heart failure, glaucoma and intraocular hypertension, cognitive dysfunction, psoriasis and any other conditions in which angiotensin II is implicated.

Compounds which have been disclosed as possessing activity as angiotensin II antagonists include compounds which are structurally related to the angiotensin II peptide, but the experimental and clinical applications of these compounds have been limited by partial agonist activity (M.A. Ondetti and D.W. Cushman, *Annual Reports in Medicinal Chemistry*, 1978, **13**, 82-91). Recently, several non-peptide compounds have been described as angiotensin II antagonists. Illustrative of such compounds are heterocyclic substituted biphenyl derivatives (D.J. Carini *et al., J. Med. Chem.*, 1991, **34**, 2525-2547; P.R. Bovy *et al., Med. Chem. Res.*, 1991, **1**, 86-94) and heterocyclic substituted benzofurans (EP-A-434,249).

The compounds that are expected to be active as angiotensin II antagonists form a subset of the compounds of general formula I. It is considered that the main structural features of compounds of general formula I that are particularly significant in providing their angiotensin II antagonist activity, are the A group and the B group. The B group is preferably a carboxylic acid or any one of the

groups claimed above for B that may serve as an acidic isostere (for example tetrazolyl). For angiotensin II receptor antagonist activity B preferably represents a -C(=O)OH group, a -C(=O)NHSO2C1-C6 alkyl group, a -C(=O)NHSO2C1-C4 perfluoroalkyl group, a tetrazolyl group or a -C(=O)NHtetrazolyl group. Although, there may be considerable variation of the nature of group A without loss of activity, the group should possess at least one -C1-C6 alkyl group, which is important for providing a lipophilic interaction with the angiotensin II receptor. It is understood that other substituents of the group A from the wide range specified above may enhance angiotensin II activity. The unit



is considered to function as a spacer element, providing an optimal spacial orientation of the A group with respect to the B group. The nature or identity of the linkage -(JqVm)Y- and the substituents R^2, R^3, and R^4 therefore is not thought to be particularly critical and any of the wide range of linkages -(JqVm)Y- and substituents R^2, R^3, and R^4 specified above may be used with retention of angiotensin II antagonist activity. Although, a preferred grouping for -(JqVm)- is a 1,4- substituted -CH2C6H4- group for angiotensin II antagonist activity.

Compounds of general formula I are potentially useful both as PAF antagonists and as antagonists of angiotensin II.

This invention also relates to methods of treatment for patients (or animals including mammalian animals raised in the dairy, meat, or fur trades, or as pets) suffering from disorders or diseases which can be attributed to PAF or to angiotensin II as previously described. More specifically, the invention relates to a method of treatment involving the administration of PAF antagonists of general formula I as the active ingredient and also to a method of treatment involving the administration of angiotensin II antagonists of general formula I as the active ingredient. In addition to the treatment of warm blooded animals such as mice, rats, horses, cattle, pigs, sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

According to a third aspect of the invention there is provided a compound of general formula I for use in human or veterinary medicine particularly in the management of diseases mediated by PAF or by angiotensin II. When used as PAF antagonists, the compounds of general formula I can be used among other things to reduce inflammation and pain, to correct respiratory, cardiovascular, and intravascular alterations or disorders, and to regulate the activation or coagulation of platelets, to correct hypotension during shock, the pathogenesis of immune complex deposition and smooth muscle contractions. When used as angiotensin II antagonists, the compounds of general formula I can be used in the treatment of conditions such as hypertension, congestive heart failure, glaucoma and intraocular hypertension, cognitive dysfunction and psoriasis although they also have potential in the treatment of other conditions.

According to a fourth aspect of the invention there is provided the use of a compound of general formula I in the preparation of an agent for the treatment or prophylaxis of PAF-mediated diseases, and/or the treatment of inflammatory disorders such as rheumatoid arthritis, osteoarthritis and eye inflammation, cardiovascular disorder, thrombocytopenia, asthma, endotoxin shock, adult respiratory distress syndrome, glomerulonephritis, immune regulation, gastric ulceration, transplant rejection, psoriasis, allergic dermatitis, urticaria, multiple sclerosis, cerebral, myocardial and renal ischemia and any other condition in which PAF is implicated.

According to a fifth aspect of the invention, there is provided the use of a compound of general formula I in the preparation of an agent for the treatment or prophylaxis of diseases and conditions mediated by angiotensin II. This includes the preparation of an agent for the treatment of the conditions mentioned above, particularly elevated blood pressure.

Compounds of general formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

According to a sixth aspect of the invention there is provided a pharmaceutical or veterinary formulation comprising a compound of general formula I and a pharmaceutically and/or veterinarily acceptable carrier. One or more

compounds of general formula I may be present in association with one or more non-toxic pharmaceutically and/or veterinarily acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occuring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for

example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the

known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical application to the skin compounds of general formula I may be made up into a cream, ointment, jelly, solution or suspension etc. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics such as the British Pharmacopoeia.

For topical applications to the eye, compounds of general formula I may be made up into a solution or suspension in a suitable sterile aqueous or non-aqueous vehicle. Additives, for instance buffers, preservatives including bactericidal and fungicidal agents, such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorohexidine, and thickening agents such as hypromellose may also be included.

Compounds of general formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

Compounds of general formula I may be used for the treatment of the respiratory tract by nasal or buccal administration of, for example, aerosols or

sprays which can disperse the pharmacological active ingredient in the form of a powder or in the form of drops of a solution or suspension. Pharmaceutical compositions with powder-dispersing properties usually contain, in addition to the active ingredient, a liquid propellant with a boiling point below room temperature and, if desired, adjuncts, such as liquid or solid non-ionic or anionic surfactants and/or diluents. Pharmaceutical compositions in which the pharmacological active ingredient is in solution contain, in addition to this, a suitable propellant, and furthermore, if necessary, an additional solvent and/or a stabiliser. Instead of the propellant, compressed air can also be used, it being possible for this to be produced as required by means of a suitable compression and expansion device.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 1.0 mg to about 3.5 g per patient per day). The dosage employed for the topical administration will, of course, depend on the size of the area being treated. For the eyes each dose will be typically in the range from 10 to 100 mg of the drug.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

It has been found that the compounds of general formula I exhibit *in vitro* and *in vivo* antagonistic activities with respect to PAF. Compounds of general formula I inhibit PAF-induced functions in both the cellular and tissue levels by

changing the PAF binding to its specific receptor site. The ability of compounds of general formula I to inhibit the binding of PAF to its specific receptor binding site on human platelet plasma membranes was measured according to Example 73. The ability of compounds of general formula I to reverse the hypotension caused by an infusion of PAF in rats was measured according Example 74.

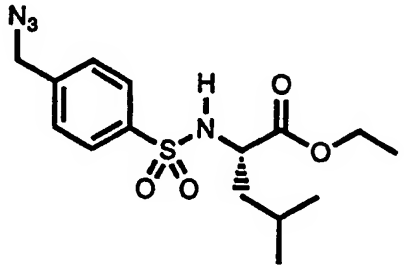
The following examples illustrate the invention, but are not intended to limit the scope in any way.
The following abbreviations have been used in the Examples:-

DCM - Dichloromethane
DIPE - Diisopropylether
DMF - Dimethylformamide
DMSO - Dimethylsulphoxide
NBS - N-Bromosuccinimide
TDA-1 - Tris(2-(2-methoxyethoxy)ethyl)amine
THF - Tetrahydrofuran

Column chromatography was performed with "flash" grade silica gel. Anhydrous magnesium sulphate or anhydrous sodium sulphate was used for drying organic solutions. Unless otherwise stated ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-250 spectrometer at 250 MHz and 62.9 MHz respectively using $CDCl_3$ as a solvent and internal reference and are reported as δ ppm from TMS.

Example 1

N-4-Azidomethylphenylsulphonyl-L-leucine ethyl ester



(a) 4-Bromomethylphenylsulphonyl chloride

To a solution of p-toluenesulphonyl chloride (50 g, 0.26 mol) in benzene (150 ml) and NBS (46.7 g, 0.26 mol) heated at reflux was added 2,2'-azobis(2-methylpropionitrile) (100 mg). The mixture was heated at reflux for 12 h and allowed to cool to room temperature. The white precipitate of succinimide that formed was separated and discarded. The filtrate was taken up in DCM (200 ml) and washed with water (3 x 100 ml) followed by brine (100 ml) and dried. Filtration, concentration and subsequent crystallisation (from DIPE) gave in two crops 4-bromomethylphenylsulphonyl chloride (46.3 g, 66%) as a white crystalline solid.

m.p. 75-76°C

δ_H 8.02 (2H, d, J 8.5 Hz), 7.64 (2H, d, J 8.5 Hz), 4.52 (2H, s).

(b) N-4-Bromomethylphenylsulphonyl-L-leucine ethyl ester

L-leucine ethyl ester hydrochloride (75.0 g. 0.403 mol) was suspended in THF (300 ml) at 0°C, and triethylamine (67 ml, 0.484 mol) added slowly. After stirring for 15 mins a solution of 4-bromomethylphenylsulphonyl chloride (108.4 g, 0.403 mol) in THF (100 ml) was added *via* cannular. The reaction mixture was allowed to stir overnight at ambient temperature. The solvent was removed under low pressure and the organics were extracted into ethyl acetate (200 ml) and washed with water (100 ml) and brine (100 ml). The organic portion was dried, filtered and the solvent evaporated under low pressure. The product was recrystallised from DIPE (500 ml) to give N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester (134 g, 85%) as a white crystalline solid.

δ_H 7.84 (2H, d, J 8.3 Hz), 7.52 (2H, d, J 8.3 Hz), 5.06 (1H, d, J 10.1 Hz), 4.61 (2H, s), 3.97-3.82 (3H, m), 1.85-1.79 (1H, m), 1.49 (2H, t, J 7.1 Hz), 1.08 (3H, t, J 7.1 Hz), 0.92 (3H, d, J 6.7 Hz), 0.91 (3H, d, J 6.5 Hz).

(c) N-4-Azidomethylphenylsulphonyl-L-leucine ethyl ester

A solution of sodium azide (75.0 g, 1.054 mol) in water (150 ml) was added to a solution of the N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester (89.0 g, 0.221 mol) in dichloromethane (150 ml). Benzyltriethylammonium chloride (10 g, 0.044 mol) was added and the heterogeneous reaction mixture stirred vigorously for 60 h. The reaction mixture was transferred to a separatory funnel, and the organic portion separated, washed thoroughly with water, dried,

filtered and concentrated to a golden oil, which crystallised on standing. The resulting white solid was freeze dried overnight to yield N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester (78.2 g, 97%) as a white solid.

m.p. 75-77°C

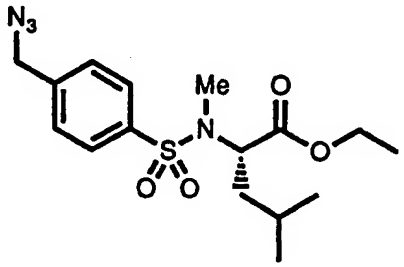
Analysis calculated for $C_{15}H_{22}N_4O_4S$
Requires C 50.83 H 6.26 N 15.81
Found C 50.80 H 6.28 N 15.82

i.r. (DCM) 2930, 2100, 1730, 1335, 1150 cm^{-1}

δ_H 7.86 (2H, d, J 8.4 Hz), 7.45 (2H, d, J 8.6 Hz), 5.13, (1H, d, J 10.0 Hz), 4.43 (2H, s), 3.98-3.84 (3H, m), 1.83-1.75 (1H, m), 1.49 (2H, dd, J 7.7, 6.7 Hz), 1.09 (3H, t, J 7.1 Hz), 0.91 (3H, d, J 6.7 Hz), 0.89 (3H, d, J 6.5 Hz).

Example 2

N-Methyl-N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester



A 60% dispersion of sodium hydride in mineral oil (9.68 g, 0.242 mol) was added in portions to a solution of N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester (78.0 g, 0.220 mol) in THF (200 ml) at 0°C. After stirring for 20 mins iodomethane (28 ml, 0.44 mol) was added slowly, and the reaction allowed to warm to ambient temperature overnight. Saturated ammonium chloride solution (ca. 15 ml) was added and the THF removed under reduced pressure. The resulting residue was taken up in dichloromethane, washed with saturated aqueous hydrogen carbonate and water, dried, filtered and concentrated to give N-methyl-N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester as an orange oil (76.0 g, 94%).

Analysis calculated for $C_{16}H_{24}N_4O_4S$

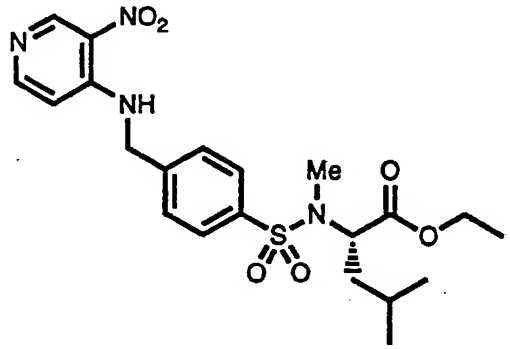
Requires C 52.16 H 6.57 N 15.21
Found C 52.20 H 6.54 N 15.12

i.r. (DCM) 2100, 1735, 1340, 1160 cm^{-1}

δ_H 7.83 (2H, dd, J 6.6, 1.6 Hz), 7.45 (2H, d, J 8.3 Hz), 4.71-4.65 (1H, m), 4.44 (2H, s), 3.96-3.86 (2H, m), 2.86 (3H, s), 1.67-1.58 (3H, m), 1.09 (3H, t, J 7.1 Hz), 0.99 (3H, d, J 5.0 Hz), 0.97 (3H, d, J 6.1 Hz).

Example 3

N-Methyl-N-4-(N'-3-nitropyrid-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester



(a) N-Methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester

Triphenylphosphine (101.80 g, 0.388 mol) was added to a solution of N-methyl-N-4-azidomethylphenylsulphonyl-L-leucine ethyl ester (71.5 g, 0.194 mol) in a mixture of THF and water (4:1, 200 ml), and the reaction mixture stirred overnight at ambient temperature. The THF was removed under reduced pressure, and the product extracted with ethyl acetate, dried, filtered and concentrated to an orange oil. This was purified by chromatography (1:2 ethyl acetate/hexane; ethyl acetate; 10% methanol in ethyl acetate) to give N-methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester (38.0 g, 58%) as a yellow oil.

δ_H 7.76 (2H, dd, J 6.8, 1.7 Hz), 7.45 (2H, d, J 8.3 Hz), 4.71-4.65 (1H, m), 3.95 (2H, s), 3.95-3.85 (2H, m), 2.83 (3H, s), 1.68-1.57 (3H, m), 1.06 (3H, t, J 7.1 Hz), 0.97 (3H, d, J 5.4 Hz), 0.95 (3H, d, J 5.9 Hz).

(b) N-Methyl-N-4-(N'-3-nitropyrid-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester

4-Chloro-3-nitropyridine (6.0 g, 38 mmol) was added to a stirred solution of N-methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester (13.0 g, 38 mmol) and triethylamine (5.3 ml, 38 mmol) in chloroform (150 ml) at ambient temperature. The reaction mixture was stirred for 60 h, then washed with water, dried, filtered and the solvent removed under reduced pressure to leave a brown oil. This was purified by chromatography (gradient elution 33% ethyl acetate in hexane to 100% ethyl acetate) to furnish N-methyl-N-4-(N'-3-nitropyrid-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester (10.9 g, 62%) as a yellow amorphous solid.

m.p. 71-75°C

Analysis calculated for $C_{21}H_{28}N_4O_6S$
Requires C 54.30 H 6.08 N 12.06
Found C 54.35 H 6.09 N 12.00

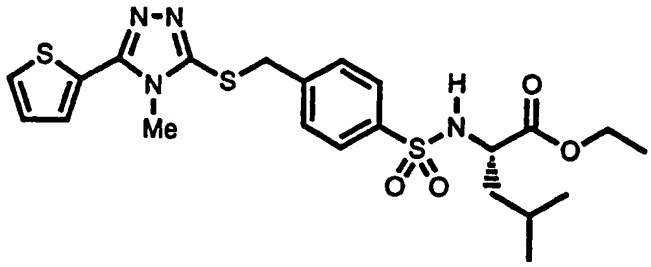
i.r. ($CDCl_3$) 3390, 1730, 1510, 1330 cm^{-1}

δ_H 9.00 (1H, s), 8.55, (1H, t, J 5.9 Hz), 8.04 (1H, d, J 6.1 Hz), 7.60 (2H, d, J 8.3 Hz) 7.32 (2H, d, J 8.3 Hz), 6.50 (1H, d, J 6.2 Hz), 4.57 (2H, d, J 5.9 Hz), 4.50-4.44 (1H, m), 3.75-3.62 (2H, m), 2.69 (3H, s), 1.45 (3H, m), 0.86 (3H, t, J 7.1 Hz), 0.77 (6H, d, J 5.9 Hz)

δ_C 170.32, 152.79, 148.25, 148.25, 148.00, 141.08, 138.13, 129.58, 127.46, 126.84, 107.80, 60.41, 56.72, 45.51, 37.55, 29.36, 23.68, 22.52, 20.60.

Example 4

N-4-(4-Methyl-5-(2-thienyl)-1,2,4-triazol-3-yl)thiomethylphenylsulphonyl-L-leucine ethyl ester



To a solution of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole (1.5 g, 7.65 mmol) in THF (60ml) at 0°C was added sodium hydride (0.306 g, 7.65 mmol) and the mixture stirred for one hour under argon. N-4-Bromomethylphenylsulphonyl-L-leucine ethyl ester (3.0 g, 7.65mmol) was

added and the stirred solution allowed to warm to room temperature overnight. Saturated ammonium chloride and ethyl acetate were added, and the organic layer separated, dried, filtered and concentrated under reduced pressure. The residue was purified by chromatography (4:1 ethyl acetate/hexane) to give N-4-(4-methyl-5-(2-thienyl)-1,2,4-triazol-3-yl)thiomethylphenylsulphonyl-L-leucine ethyl ester as a white solid (3.27 g, 84%).

m.p. 90°C

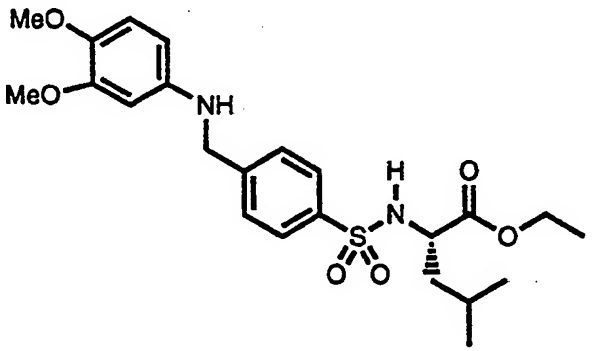
i.r. ($CDCl_3$) 1730, 1340, 1160 cm^{-1}

δ_H 7.70 (2H, d, 8.5 Hz), 7.47-7.34 (4H, m), 7.10-7.04 (1H, m), 5.58 (1H, d, J 9.9 Hz), 4.40 (2H, s), 3.90-3.75 (1H, m), 3.76 (2H, q, J 7.1 Hz), 3.46 (3H, s), 1.78-1.63 (1H, m), 1.48-1.37 (2H, m), 0.99 (3H, t, J 7.0 Hz), 0.81 (3H, d, J 6.9 Hz), 0.78 (3H, d, J 6.6 Hz).

δ_C 172.04, 150.50, 142.27, 139.20, 129.59, 128.47, 127.87, 127.77, 127.59, 61.47, 54.43, 42.28, 37.21, 31.57, 24.24, 22.66, 21.34, 13.89.

Example 5

N-4-(N'-3,4-Dimethoxyphenyl)aminomethylphenylsulphonyl-L-leucine ethyl ester



N-4-(N'-3,4-Dimethoxyphenyl)aminomethylphenylsulphonyl-L-leucine ethyl ester was prepared by the procedure of Example 4 employing 3,4-dimethoxyaniline *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole.

Colourless oil (38% yield after chromatography (2:1 ethyl acetate/hexane)):

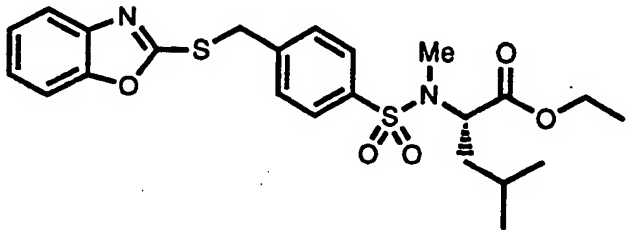
i.r. ($CDCl_3$) 1730, 1340, 1150 cm^{-1}

δ_H 7.77 (2H, d, J 8.4 Hz), 7.47 (2H, d, J 8.3 Hz), 6.67 (1H, d, J 8.6 Hz), 6.26 (1H, d, J 2.6 Hz), 6.07 (1H, dd J 8.6, 2.7 Hz), 5.24 (1H, d, J 10.0 Hz), 4.36 (2H, s), 3.98-3.70 (4H, m), 3.79 (3H, s), 3.77 (3H, s), 1.84-1.69 (1H, m), 1.54-1.40 (2H, m), 1.04 (3H, t, J 7.2 Hz), 0.88 (3H, d, J 6.7 Hz), 0.88 (3H, d, J 6.5 Hz).

δ_C 172.94, 150.83, 145.64, 144.08, 143.14, 142.17, 139.38, 113.87, 105.09, 100.39, 62.34, 59.09, 56.74, 55.21, 49.52, 43.09, 25.32, 23.03, 22.28.

Example 6

N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucine ethyl ester



(a) N-Methyl-N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester

N-4-Bromomethylphenylsulphonyl-L-leucine ethyl ester (2.0 g, 5.1 mmol) was dissolved in dry THF (30 ml) under argon and cooled to 0°C. Sodium hydride (60% dispersion in oil: 200 mg, 5.1 mmol) was added followed by methyl iodide (0.64 ml, 10.2 mmol) after a period of 5 mins. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (30 ml) and extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were washed with brine (50 ml), dried, filtered and evaporated to give N-methyl-N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester as an orange oil which was used directly in the next step without further purification.

δ_H 7.81 (2H, d, J 8.5 Hz), 7.52 (2H, d, J 8.5 Hz), 4.66 (1H, dd, J 9.3, 7.4 Hz), 4.62 (2H, s), 3.99-3.79 (2H, m), 2.87 (3H, s), 1.74-1.58 (3H, m), 1.07 (3H, t, J 7.3 Hz), 0.99 (3H, d, J 5.2 Hz), 0.97 (3H, d, H, J 6.0 Hz).

(b) N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucine ethyl ester

N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucine ethyl ester was prepared by the procedure of Example 4 employing 2-

mercaptobenzoxazole *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole and N-methyl-N-4-bromomethyl-phenylsulphonyl-L-leucine ethyl ester *in lieu* of N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester.

Pale yellow oil (15% yield after chromatography (1:3 ethyl acetate/hexane)):

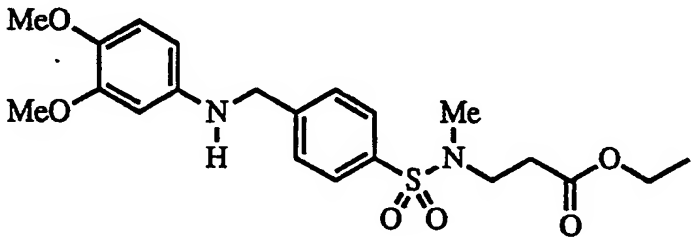
i.r. ($CDCl_3$) 1735, 1350, 1140 cm^{-1}

δ_H 7.74 (2H, d, J 8.5 Hz), 7.63-7.54 (3H, m), 7.46-7.40 (1H, m), 7.32-7.16 (2H, m), 4.61 (1H, t, J 7.4 Hz), 4.55 (2H, s), 3.90-3.64 (2H, m), 2.82 (3H, s), 1.70-1.53 (3H, m), 1.00-0.86 (9H, m);

δ_C 170.53, 163.33, 151.63, 141.42, 141.25, 138.26, 129.37, 127.40, 124.26, 123.66, 118.22, 109.65, 60.56, 56.94, 37.84, 35.31, 29.59, 24.07, 22.75, 20.89.

Example 7

N-Methyl-N-4-(N'-3,4-dimethoxyphenyl)aminomethylphenylsulphonyl-3-amino-propionic acid ethyl ester



N-Methyl-N-4-(N'-3,4-dimethoxyphenyl)aminomethylphenylsulphonyl-3-amino-propionic acid ethyl ester was prepared by the methods of Example 1 Step (b) and Example 6 employing β-alanine ethyl ester hydrochloride as starting material and 3,4-dimethoxyaniline in the final step.

White crystalline solid (50% yield for last step after chromatography (2:1 ethyl acetate/hexane)): m.p. 113°C

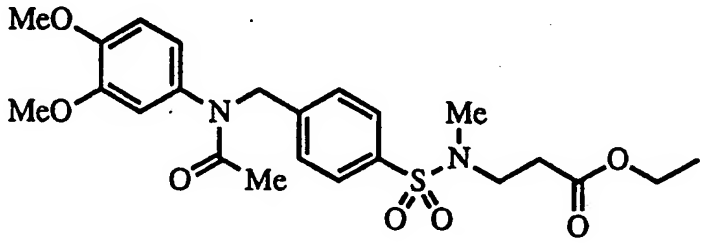
Analysis calculated for $C_{21}H_{28}N_2O_6S$
Requires C 57.78 H 6.47 N 6.42
Found C 57.90 H 6.53 N 6.42

i.r. ($CDCl_3$) 1720, 1335, 1170 cm^{-1}

δ_H 7.74 (2H, d, J 8.3 Hz), 7.53 (2H, d, J 8.3 Hz), 6.71 (1H, d, J 8.5 Hz), 6.27 (1H, d, J 2.6 Hz), 6.09 (1H, dd, J 8.5, 2.5 Hz), 4.39 (2H, s), 4.14 (2H, q, J 7.1 Hz), 3.80 (3H, s), 3.79 (3H, s), 3.32 (2H, t, J 7.2 Hz), 2.78 (3H, s), 2.61 (2H, t, J 7.2 Hz), 1.26 (3H, t, 7.2 Hz).

Example 8

N-Methyl-N-4-(N'-(3,4-dimethoxyphenyl)-N'-acetyl)aminomethylphenyl-sulphonyl-3-aminopropionic acid ethyl ester



N-Methyl-N-4-(N'-3,4-dimethoxyphenyl)aminomethylphenylsulphonyl-3-amino-propionic acid ethyl ester (1.0 g, 2.3 mmol) was treated with acetic anhydride (432 µl, 4.6 mmol) in the presence of 4-dimethylaminopyridine (10 mg) and pyridine (196 µl, 2.4 mmol) in dry DCM (60 ml) at 0°C. The mixture was allowed to warm up to room temperature and was stirred for 2 h. The products were treated with saturated aqueous ammonium chloride, extracted into ethyl acetate and evaporated under reduced pressure to yield an oil. Chromatography (1.5:1 ethyl acetate/hexane) gave N-methyl-N-4-(N'-(3,4-dimethoxyphenyl)-N'-acetyl)aminomethylphenylsulphonyl-3-aminopropionic acid ethyl ester as a clear colourless oil (0.62 g, 60%).

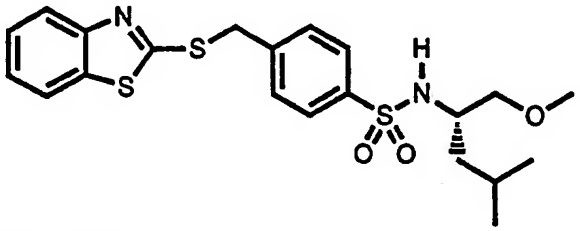
i.r. ($CDCl_3$) 1725, 1650 cm^{-1}

δ_H 7.63 (2H, d, J 8.3 Hz), 7.32 (2H, d, J 8.3 Hz), 6.72 (1H, d, J 8.3 Hz), 6.50-6.40 (2H, m), 4.84 (2H, s), 4.06 (2H, q, J 7.2 Hz), 3.80 (3H, s), 3.70 (3H, s), 3.24 (2H, t, J 7.2 Hz), 2.70 (3H, s), 2.53 (2H, t, J 7.2 Hz), 1.85 (3H, s), 1.18 (3H, t, J 7.2 Hz);

δ_C 171.06, 170.97, 149.48, 148.74, 142.82, 136.32, 135.25, 129.37, 127.74, 120.27, 111.21, 110.87, 60.69, 60.25, 55.88, 52.36, 46.04, 35.70, 35.49, 22.31, 20.90.

Example 9

N-4-(Benzthiazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl methyl ether



(a) L-leucinyl methyl ether

Sodium hydride (60% dispersion in oil: 9.39 g, 0.24 mol) was added to a stirred solution of L-leucinol (25 ml, 0.20 mol) in a mixture of dry acetonitrile (12 ml) and dry THF (60 ml) at room temperature under argon. The mixture was heated at reflux for 2 h, cooled to 55°C and methyl iodide (12.8 ml, 2.1 mol) carefully added. The reaction mixture was heated at reflux overnight and allowed to cool to room temperature. Ice cold brine (100 ml) was added carefully and the mixture extracted with ethyl acetate (3x100 ml). The combined organic extracts were dried, filtered and evaporated. The residue was distilled under reduced pressure to give L-leucinyl methyl ether as a colourless oil which was used directly in the next step.

(b) N-4-Bromomethylphenylsulphonyl-L-leucinyl methyl ether

N-4-Bromomethylphenylsulphonyl-L-leucinyl methyl ether was prepared following the procedure of Example 1 Step (b) utilising L-leucinyl methyl ether *in lieu* of L-leucine ethyl ester.

Colourless oil (37% yield over Steps (a) and (b)).

δ_H 7.92-7.83 (2H, m), 7.58-7.50 (2H, m), 4.74 (1H, br d, J 9.4 Hz), 4.62, 4.50 (2H, 2s), 3.50-3.38 (1H, m), 3.20 (1H, dd, J 9.4, 3.0 Hz), 3.17 (3H, s), 3.14 (1H, dd, J 9.4, 3.8 Hz), 1.60-1.48 (1H, m), 1.46-1.20 (2H, m), 0.85 (3H, d, J 7.5 Hz), 0.75 (3H, d, J 7.3 Hz).

(c) N-4-(Benzthiazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl methyl ether

N-4-(Benzthiazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl methyl ether was prepared by the procedure of Example 2 employing 2-mercaptobenzthiazole *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole and N-4-bromomethylphenylsulphonyl-L-leucinyl methyl ether *in lieu* of N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester.

Straw yellow oil (16% yield after chromatography (1:3 ethyl acetate/hexane)):

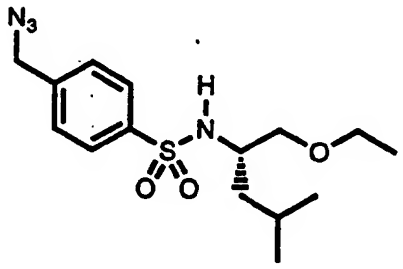
i.r. ($CDCl_3$) 3050-2800, 1500, 1340, 1160 cm^{-1}

δ_H 7.84 (2H, d, J 8.5 Hz), 7.65-7.56 (3H, m), 7.46-7.40 (1H, m), 7.33-7.20 (2H, m), 4.71 (1H, d, J 8.6 Hz), 4.59 (2H, s), 3.44-3.30 (1H, m), 3.16 (1H, dd, J 9.5, 4.3 Hz), 3.10-3.02 (1H, m), 3.08 (3H, s), 1.58-1.42 (1H, m), 1.40-1.16 (2H, m), 0.77 (3H, d, J 6.5 Hz), 0.69 (3H, d, J 6.5 Hz);

δ_C 151.94, 141.39, 140.70, 129.58, 127.43, 124.43, 118.54, 109.93, 74.02, 58.84, 51.86, 41.62, 35.71, 24.29, 22.75, 21.78.

Example 10

N-4-Azidomethylphenylsulphonyl-L-leucinyl ethyl ether



(a) L-Leucinyl ethyl ether

L-Leucinyl ethyl ether was prepared by the procedure of Example 9 Step (a) employing ethyl iodide *in lieu* of methyl iodide.

Colourless oil (30% yield):

δ_H 3.49-3.14 (4H, m), 3.08-2.81 (2H, m), 1.73-1.50 (1H, m), 1.16-0.91 (6H, m), 0.84 (3H, d, J 6.9 Hz), 0.81 (3H, d, J 6.7 Hz).

(b) N-4-Bromomethylphenylsulphonyl-L-leucinyl ethyl ether

N-4-Bromomethylphenylsulphonyl-L-leucinyl ethyl ether was prepared by the procedure of Example 9 Step (b) employing L-leucinyl ethyl ether *in lieu* of L-leucinyl methyl ether.

White crystalline solid (68% yield): m.p. 70°C

i.r. ($CDCl_3$) 3380, 2960, 2870, 1410, 1365, 1155, 1115 cm^{-1}

δ_H 7.85 (2H, d, J 8.4 Hz), 7.49 (2H, d, J 8.3 Hz), 5.02 (1H, d, J 8.4 Hz), 4.48 (2H, s), 3.47-3.20 (5H, m), 1.56 (1H, m), 1.45-1.20 (2H, m), 1.04 (3H, t, J 7.0 Hz), 0.82 (3H, d, J 6.6 Hz), 0.74 (3H, d, J 6.5 Hz).

(c) N-4-Azidomethylphenylsulphonyl-L-leucinyl ethyl ether

N-4-Azidomethylphenylsulphonyl-L-leucinyl ethyl ether was prepared by the procedure of Example 1 Step (c) employing N-4-bromomethylphenylsulphonyl-L-leucinyl ethyl ether as starting material.

White amorphous solid (98% yield).

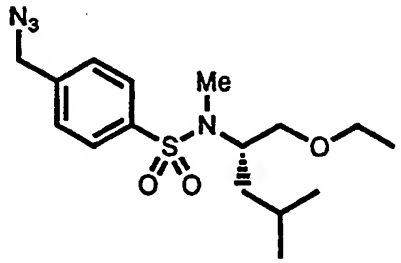
i.r. (DCM) 3370, 2865, 1335, 1150 cm^{-1}

δ_H 7.91 (2H, d, J 8.4 Hz), 7.46 (2H, d, J 8.6 Hz), 4.86 (1H, d, J 8.6 Hz), 4.44 (2H, s), 3.45-3.13 (5H, m), 1.63-1.50 (1H, m), 1.47-1.22 (2H, m), 1.08 (3H, t, J 7.1 Hz), 0.84 (3H, d, J 6.6 Hz), 0.77 (3H, d, J 6.5 Hz).

δ_C 141.27, 140.08, 126.43, 127.59, 71.74, 66.61, 53.96, 52.04, 41.79, 24.35, 22.78, 21.94, 14.89.

Example 11

N-Methyl-N-4-azidomethylphenylsulphonyl-L-leucinyl ethyl ether



N-Methyl-N-4-azidomethylphenylsulphonyl-L-leucinyl ethyl ether was prepared by the procedure of Example 2 employing N-4-azidomethylphenylsulphonyl-L-leucinyl ethyl ether as starting material.

Orange oil (98% yield).

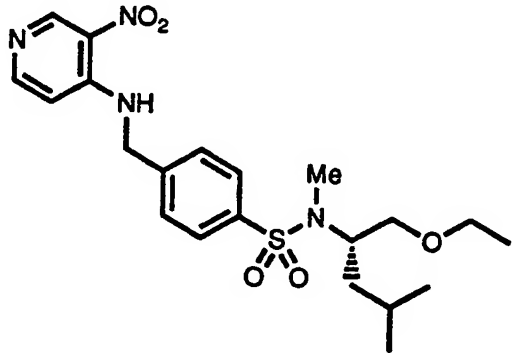
i.r. (DCM) 2865, 1335, 1145 cm^{-1}

δ_H 7.87 (2H, d, J 8.4 Hz), 7.42 (2H, d, J 8.3 Hz), 4.42 (2H, s), 4.24-4.11 (1H, m), 3.36-3.18 (4H, m), 2.73 (3H, s), 1.66-1.52 (1H, m), 1.41-1.15 (2H, m), 0.99 (3H, t, J 7.0 Hz), 0.93 (3H, d, J 6.5 Hz), 0.91 (3H, d, J 6.6 Hz).

δ_C 140.30, 139.68, 128.11, 128.06, 70.99, 66.32, 54.92, 54.05, 36.06, 28.51, 24.41, 23.19, 22.00, 14.70.

Example 12

N-Methyl-N-4-(N'-3-nitropyrid-4-yl)aminomethylphenylsulphonyl-L-leucinyl ethyl ether



(a) N-Methyl-N-4-aminomethylphenylsulphonyl-L-leucinyl ethyl ether

N-Methyl-N-4-aminomethylphenylsulphonyl-L-leucinyl ethyl ether was prepared by the procedure of Example 3 Step (a) employing N-methyl-N-4-azidomethylphenylsulphonyl-L-leucinyl ethyl ether as starting material.

Yellow oil (68% yield):

δ_H 7.81 (2H, d, J 8.3 Hz), 7.43 (2H, d, J 8.3 Hz), 4.24-4.13 (1H, m), 3.95 (2H, s), 3.39-3.19 (4H, m), 2.70 (3H, s), 1.65-1.51 (1H, m), 1.39-1.15 (2H, m), 1.00 (3H, t, J 7.0 Hz), 0.92 (3H, d, J 6.4 Hz), 0.89 (3H, d, J 6.9 Hz).

(b) N-Methyl-N-4-(N'-3-nitropyrid-4-yl)aminomethylphenylsulphonyl-L-leucinyl ethyl ether

N-Methyl-N-4-(N'-3-nitropyrid-4-yl)aminomethylphenylsulphonyl-L-leucinyl ethyl ether was prepared by the procedure of Example 3 Step (b) employing N-methyl-N-4-aminomethylphenylsulphonyl-L-leucinyl ethyl ether as starting material.

Yellow crystalline solid (63% yield): m.p. 129-130 C

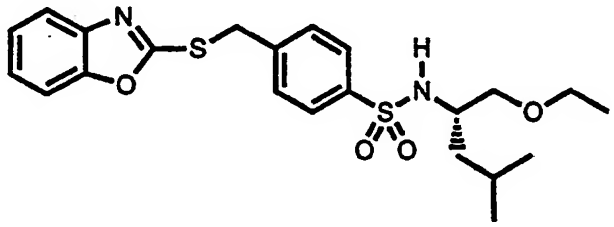
i.r. (DCM) 3390, 1610, 1520, 1345, 1150 cm^{-1}

δ_H 9.25 (1H, s), 8.62-8.57 (1H, br m), 8.27 (1H, d, J 5.9 Hz), 7.87 (2H, d, J 8.4 Hz), 7.42 (2H, d, J 8.3 Hz), 6.63 (1H, d, J 6.2 Hz), 4.65 (2H, d, J 5.9 Hz), 4.24-4.13 (1H, m), 3.37-3.16 (4H, m), 2.72 (3H, s), 1.65-1.51 (1H, m), 1.40-1.13 (2H, m), 0.95 (3H, t, J 7.0 Hz), 0.91 (3H, d, J 6.4 Hz), 0.90 (3H, d, J 6.6 Hz).

δ_C 153.27, 148.86, 148.52, 140.44, 140.00, 128.43, 127.08, 108.02, 70.95, 66.29, 54.96, 46.29, 38.06, 28.44, 24.41, 23.01, 22.00.

Example 13

N-4-(Benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl ethyl ether



N-4-(Benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl ethyl ether was prepared by the procedure of Example 4 employing 2-mercaptobenzoxazole *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole and N-4-bromomethylphenylsulphonyl-L-leucinyl ethyl ether *in lieu* of N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester.

White crystalline solid (34% yield after chromatography (30% ethyl acetate in hexane) and crystallisation from ethyl acetate): m.p. 87°C

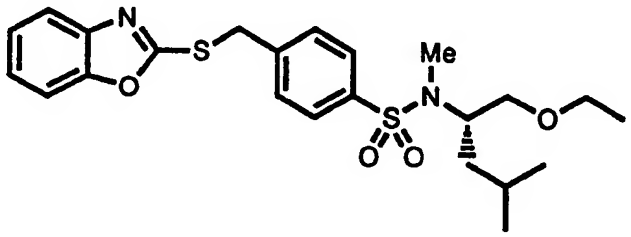
i.r. ($CDCl_3$) 3380, 2960, 2870, 1600, 1495, 1410, 1130 cm^{-1}

δ_H 7.84 (2H, d, J 8.5 Hz), 7.66-7.56 (3H, m), 7.47-7.40 (1H, m), 7.33-7.20 (2H, m), 4.81 (1H, d, J 8.6 Hz), 4.58 (2H, s), 3.46-3.28 (1H, m), 3.30-3.06 (4H, m), 1.61-1.47 (1H, m), 1.50-1.16 (2H, m), 1.01 (3H, t, J 7.2 Hz), 0.79 (3H, d, J 6.6 Hz), 0.70 (3H, d, J 6.4 Hz);

δ_C 163.56, 151.93, 141.64, 141.27, 140.76, 129.58, 127.43, 124.45, 124.18, 118.53, 109.95, 71.68, 66.51, 51.98, 41.79, 35.71, 24.31, 22.77, 21.85, 14.86.

Example 14

N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl ethyl ether



(a) N-Methyl-N-4-bromomethylphenylsulphonyl-L-leucinyl ethyl ether

Sodium hydride (60% dispersion in oil: 0.31 g, 7.9 mmol) was added to a stirred solution of N-4-bromomethylphenylsulphonyl-L-leucinyl ethyl ether (2.50 g, 6.6 mmol) in dry THF (50 ml) at 0°C under argon. The solution was allowed to warm up to room temperature and was stirred for 1 h. Methyl iodide (0.82 ml, 13.2 mmol) was added dropwise and the mixture stirred overnight. The solvent was evaporated under reduced pressure and the organics extracted with ethyl acetate (100 ml) and washed with water (100 ml) and brine (100 ml). The organics were dried, filtered and evaporated to give N-methyl-N-4-bromomethylphenylsulphonyl-L-leucinyl ethyl ether as a yellow oil (2.46 g, 95%).

δ_H 7.84 (2H, d, J 8.3 Hz), 7.46 (2H, d, J 8.3 Hz), 5.30 (2H, s), 4.16 (1H, m), 3.37-3.20 (4H, m), 2.71 (3H, s), 1.61 (1H, m), 1.40-1.15 (2H, m), 0.98 (3H, t, J 7.0 Hz), 0.93 (3H, d, J 6.5 Hz), 0.91 (3H, d, J 6.6 Hz).

(b) N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl ethyl ether

N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl ethyl ether was prepared by the procedure of Example 4 employing 2-mercaptobenzoxazole *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole and N-methyl-N-4-bromomethylphenylsulphonyl-L-leucinyl ethyl ether *in lieu* of N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester.

Colourless oil (25% yield after chromatography (1:1 ethyl acetate/hexane)):

i.r. ($CDCl_3$) 3000-2800, 1340, 1120 cm^{-1}

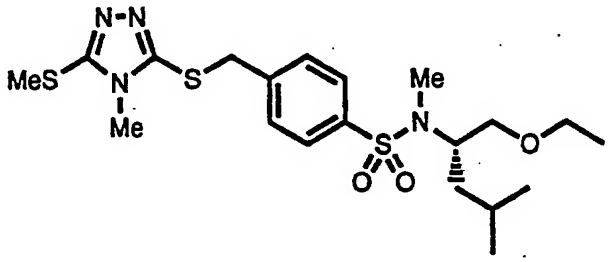
δ_H 7.82 (2H, d, J 8.5 Hz), 7.64-7.56 (3H, m), 7.46-7.40 (1H, m), 7.33-7.20 (2H, m), 4.58 (2H, s), 4.20-4.08 (1H, m), 3.22-3.12 (4H, m), 2.71 (3H, s), 1.65-1.50 (1H, m), 1.40-1.10 (2H, m), 0.94-0.84 (9H, m);

δ_C 163.68, 151.91, 141.70, 140.63, 139.83, 129.24, 127.67, 124.38, 124.08, 118.50, 109.90, 70.90, 66.20, 54.84, 38.03, 35.72, 28.45, 24.35, 23.16, 21.94, 14.83.

Examples 15-17

The compounds of Examples 15-17 were prepared by the procedure of Example 4 employing the appropriate thiol or amine *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole and N-methyl-N-4-bromomethylphenylsulphonyl-L-leucinyl ethyl ether *in lieu* of N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester.

15. N-Methyl-N-4-(4-methyl-5-methylthio-1,2,4-triazol-3-yl)thiomethylphenyl-sulphonyl-L-leucinyl ethyl ether



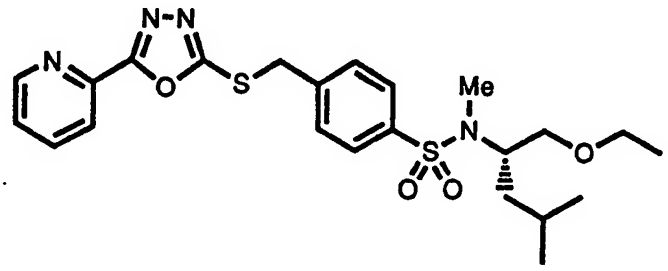
Pale yellow oil (38% yield after chromatography (ethyl acetate)):

i.r. ($CDCl_3$) 3100-2700, 1400, 1100 cm^{-1}

δ_H 7.72 (2H, d, J 8.4 Hz), 7.38 (2H, d, J 8.3 Hz), 4.34 (2H, s), 4.20-4.06 (1H, m), 3.30-3.14 (4H, m), 3.21 (3H, s), 2.65 (3H, s), 2.64 (3H, s), 1.62-1.50 (1H, m), 1.38-1.10 (2H, m), 0.92 (3H, t, J 7.1 Hz), 0.86 (3H, d, J 6.4 Hz), 0.85 (3H, d, J 6.6 Hz).

δ_C 153.09, 150.31, 141.30, 139.64, 129.17, 127.74, 70.90, 66.20, 54.74, 37.96, 37.31, 30.05, 28.38, 24.31, 23.12, 21.90, 14.95, 14.83.

16. N-4-(5-(2-Pyridyl)-1,3,4-oxadiazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl ethyl ether



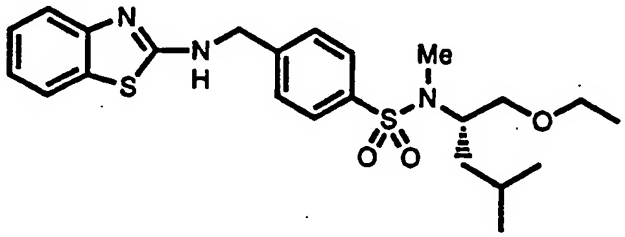
Pale yellow oil (26% yield after chromatography (ethyl acetate/hexane)):

i.r. ($CDCl_3$) 3000-2840, 1590, 1330, 1150 cm^{-1}

δ_H 8.76-8.71 (1H, m), 8.20-8.13 (1H, m), 7.90-7.78 (3H, m), 7.62-7.54 (2H, d, J 8.3 Hz), 7.48-7.40 (1H, m), 4.56 (2H, s), 4.21-4.06 (1H, m), 3.30-3.10 (4H, m), 2.69 (3H, s), 1.64-1.50 (1H, m), 1.38-1.10 (2H, m), 0.97-0.85 (9H, m).

δ_C 164.91, 164.68, 150.09, 142.86, 139.89, 137.17, 129.28, 127.77, 125.75, 122.67, 70.71, 66.08, 54.74, 37.88, 35.73, 28.29, 24.21, 23.04, 21.81, 14.71.

17. N-Methyl-N-4-(N'-benzthiazol-2-yl)aminomethylphenylsulphonyl-L-leucinyl ethyl ether



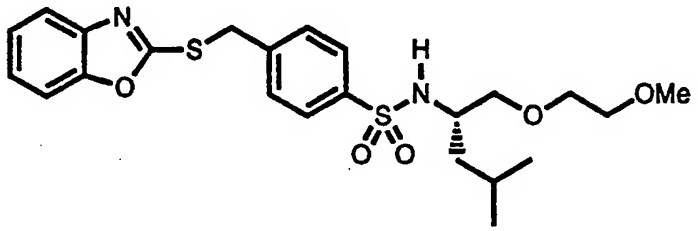
Straw yellow oil (19% yield after chromatography (1:3 ethyl acetate/hexane)):

i.r. ($CDCl_3$) 3000-2800, 1600, 1330, 1150 cm^{-1}

δ_H 7.75 (2H, d, J 8.4 Hz), 7.42-7.33 (1H, m), 7.30-7.08 (5H, m), 6.99-6.90 (1H, m), 4.28-4.14 (1H, m), 3.89 (2H, s), 3.40-3.26 (4H, m), 2.69 (3H, s), 1.67-1.52 (1H, m), 1.40-1.14 (2H, m), 1.03 (3H, t, J 6.9 Hz), 0.93 (3H, d, J 6.4 Hz), 0.92 (3H, d, J 6.7 Hz).

Example 18

N-4-(Benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl methoxyethyl ether



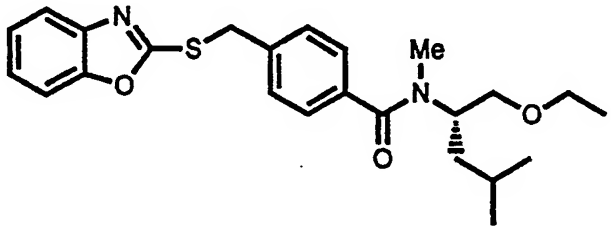
N-4-(Benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl methoxyethyl ether was prepared by the procedure of Example 9 employing 2-bromoethyl methyl ether *in lieu* of methyl iodide and 2-mercaptobenzoxazole in the last step.

Colourless oil (9.5% yield for last step after chromatography (1:2 ethyl acetate/hexane)):

δ_H 7.85 (2H, d, J 8.4 Hz), 7.66-7.56 (3H, m), 7.48-7.42 (1H, m), 7.34-7.20 (2H, m), 5.13, (1H, br d, J 8.1 Hz), 4.59 (2H, s), 3.49-3.13 (10H, m), 1.60-1.18 (3H, m), 0.79 (3H, d, J 6.6 Hz), 0.70 (3H, d, J 6.4 Hz).

Example 19

N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylcarbonyl-L-leucinyl ethyl ether



(a) 4-Bromomethylbenzoylchloride

To a solution of p-toluoyl chloride (155 g, 1 mol) in carbon tetrachloride (800 ml) and NBS (200 g, 1.1 mol) heated at reflux was added 2,2'-azobis(2-methylpropionitrile) (150 mg). The mixture was heated at reflux for 12 h and allowed to cool to room temperature. The white precipitate of succinimide that formed was separated and discarded. Concentration and subsequent

crystallisation (from DIPE at -15°C) gave in five crops 4-bromomethylbenzoyl chloride (75 g, 32%) as a white crystalline solid.

m.p. 54°C

δ_H (250MHz, $CDCl_3$) 8.11 (2H, d, J 8.3 Hz), 7.54 (2H, d, J 8.3 Hz), 4.51 (2H, s).

(b) N-Methyl-N-4-bromomethylphenylcarbonyl-L-leucinyl ethyl ether

N-Methyl-N-4-bromomethylphenylcarbonyl-L-leucinyl ethyl ether was prepared by the procedure of Example 1 Step (b) and Example 6 Step (a) employing 4-bromomethylbenzoyl chloride and leucine ethyl ether as starting materials. N-Methyl-N-4-bromomethylphenylcarbonyl-L-leucinyl ethyl ether was used without purification directly in the next step.

(c) N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylcarbonyl-L-leucinyl ethyl ether

N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylcarbonyl-L-leucinyl ethyl ether was prepared by the procedure of Example 4 employing 2-mercaptobenzoxazole *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole and N-methyl-N-4-bromomethylphenylcarbonyl-L-leucinyl ethyl ether *in lieu* of N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester.

Yellow oil (34% yield for last step after chromatography (1:2 ethyl acetate/hexane):

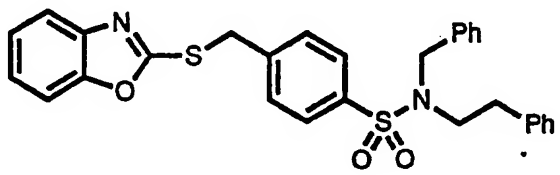
i.r. ($CDCl_3$) 2860, 1600 cm^{-1}

δ_H 7.62-7.20 (8H, m), 5.04-4.90 (0.4H, m), 4.56 (2H, s), 4.00-3.85 (0.6H, m), 3.67-3.35 (3.4H, m), 3.27 (0.6H, dd, J 10.1, 4.5 Hz), 2.91 (1.8H, s), 2.78 (1.2H, s), 1.70-0.94 (3H, m), 1.19 (1.8H, t, J 7.0 Hz), 1.18 (1.2H, t, J 7.0 Hz), 0.99 (1.2H, d, J 6.2 Hz), 0.97 (1.2H, d, J 6.1 Hz), 0.77 (1.8H, d, J 6.3 Hz), 0.58 (1.8H, d, J 6.3 Hz);

δ_C 172.50, 164.20, 151.90, 148.60, 141.80, 137.07, 136.73, 136.64, 129.03, 128.81, 127.81, 127.15, 124.30, 124.00, 118.45, 109.67, 70.93, 70.55, 66.70, 66.23, 56.15, 50.42, 38.28, 37.10, 36.18, 32.37, 26.65, 25.07, 24.29, 23.37, 23.06, 22.19, 15.21, 15.08.

Example 20

N-Benzyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-2-phenylethylamine



(a) N-Benzyl-N-4-bromomethylphenylsulphonyl-2-phenylethylamine

N-Benzyl-N-4-bromomethylphenylsulphonyl-2-phenylethylamine was prepared by the procedure of Example 1 Step (b) employing N-benzylethylamine *in lieu* of L-leucine ethyl ester hydrochloride.

White crystalline solid:

δ_H 7.80 (2H, d, J 8.5 Hz), 7.52 (2H, d, J 8.5 Hz), 7.37-7.12 (8H, m), 6.98-6.90 (2H, m), 4.51 (2H, s), 4.36 (2H, s), 3.32 (2H, dd, J 8.3, 7.9 Hz), 2.65 (2H, dd, J 8.3, 7.9 Hz).

(b) N-Benzyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-2-phenylethylamine

N-Benzyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-2-phenylethylamine was prepared by the procedure of Example 4 employing 2-mercaptobenzoxazole *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole and N-benzyl-N-4-bromomethylphenylsulphonyl-2-phenylethylamine *in lieu* of N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester.

White crystalline solid (43% yield after chromatography (1:2 ethyl acetate/hexane)): m.p. 115°C

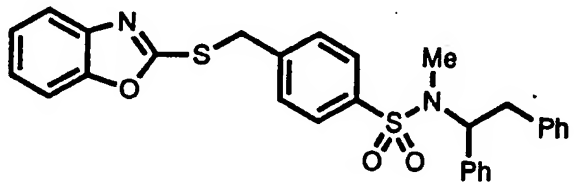
Analysis calculated for $C_{29}H_{26}N_2O_3S_2$
Requires C 67.68 H 5.09 N 5.44
Found C 67.53 H 5.15 N 5.40

i.r. ($CDCl_3$) 3015, 2935, 2240, 1600, 1500, 1345, 1130 cm^{-1}

δ_H 7.79 (2H, d, J 8.5 Hz), 7.62 (2H, d, J 8.5 Hz), 7.48-7.42 (1H, m), 7.38-7.12 (11H, m), 6.97-6.89 (2H, m), 4.60 (2H, s), 4.34 (2H, s), 3.33 (2H, t, J 8.1 Hz), 2.62 (2H, t, 8.1 Hz).

Example 21

N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-1,2-diphenyl-ethylamine



(a) N-4-Bromomethylphenylsulphonyl-1,2-diphenylethylamine

A solution of 4-bromomethylphenylsulphonyl chloride (6.82 g, 25 mmol) in dry THF (30 ml) was added to a stirred mixture of 1,2-diphenylethylamine (4.9 ml, 25 mmol) and triethylamine (3.8 ml, 25 mmol) in dry THF (20 ml) at room temperature under argon. The mixture was stirred overnight and the solvent removed under reduced pressure. The residue was extracted with ethyl acetate (100 ml), the organics washed with water (100 ml) and brine (100 ml), dried, filtered and concentrated. Chromatography (10% methanol in DCM) followed by crystallisation from ethyl acetate/hexane gave N-4-bromomethylphenylsulphonyl-1,2-diphenylethylamine (7.6 g, 69%) as a white crystalline solid.

δ_H 7.55-6.90 (14H, m), 5.45 (1H, d, J 6.1 Hz), 4.54 (2H, s), 3.91-3.89 (1H, m), 3.03-2.98 (2H, m).

(b) N-Methyl-N-4-bromomethylphenylsulphonyl-1,2-diphenylethylamine

Sodium hydride (60% dispersion in oil: 190 mg, 4.7 mmol) was added to a stirred solution of N-4-bromomethylphenylsulphonyl-1,2-diphenylethylamine (2.00 g, 4.7 mmol) in dry THF (50 ml) at 0°C under argon. Methyl iodide (0.6 ml, 9.3 mmol) was added immediately to the reaction mixture. The mixture was stirred for 48 h at ambient temperature. Saturated aqueous ammonium chloride (50 ml) was added and the mixture extracted with ethyl acetate (2x80 ml). The combined organics were washed with brine (50 ml), dried, filtered

and concentrated to give N-methyl-N-4-bromomethylphenylsulphonyl-1,2-diphenylethylamine as an orange oil which was used directly in the next step.

δ_H 7.45-7.10 (14H, m), 5.57 (1H, dd, J 8.9, 6.9 Hz), 4.39 (2H, s), 3.29 (1H, dd, J 14.1, 6.8 Hz), 3.08 (1H, dd, J 14.1, 9.0 Hz), 2.69 (3H, s).

(c) N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-1,2-diphenylethylamine

N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-1,2-diphenylethylamine was prepared by the procedure of Example 4 employing 2-mercaptobenzoxazole *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole and N-methyl-N-4-bromomethylphenylsulphonyl-1,2-diphenylethylamine *in lieu* of N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester.

White crystalline solid (36% yield after chromatography (1:3 ethyl acetate/hexane)): m.p. 102°C

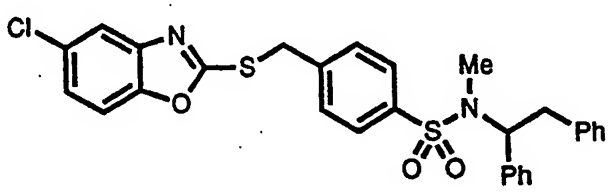
Analysis calculated for $C_{29}H_{26}N_2O_3S_2$
Requires C 66.91 H 5.21 N 5.57
Found C 66.72 H 5.18 N 5.17

i.r. ($CDCl_3$) 3100-2800, 1500, 1340, 1160 cm^{-1}

δ_H 7.68-7.62 (1H, m), 7.50-7.10 (17H, m), 5.57 (1H, dd, J 8.9, 6.8 Hz), 4.53 (2H, s), 3.25 (1H, dd, J 14.1, 6.7 Hz), 3.05 (1H, dd, J 14.1, 9.1 Hz), 2.66 (3H, s).

Example 22

N-Methyl-N-4-(5-chlorobenzoxazol-2-yl)thiomethylphenylsulphonyl-1,2-diphenylethylamine



N-Methyl-N-4-(5-chlorobenzoxazol-2-yl)thiomethylphenylsulphonyl-1,2-diphenylethylamine was prepared by the procedure of Example 4 employing 2-mercapto-5-chlorobenzoxazole *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole and N-methyl-N-4-bromomethylphenylsulphonyl-1,2-diphenylethylamine *in lieu* of N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester.

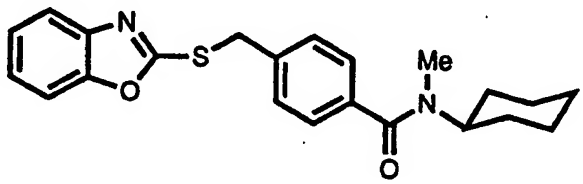
White crystalline solid (22% yield after chromatography (1:3 ethyl acetate/hexane) and crystallisation from DCM/hexane):

Analysis calculated for $C_{29}H_{25}ClN_2O_3S_2.1.4\ H_2O$
Requires C 60.65 H 4.88 N 4.88
Found C 60.28 H 4.48 N 4.81

δ_H 7.90 (1H, d, J 1.9 Hz), 7.66 (1H, d, J 8.6 Hz), 7.45-7.07 (15H, m), 5.56 (1H, dd, J 8.8, 6.9 Hz), 4.59 (2H, s), 3.25 (1H, dd, J 14.2, 6.9 Hz), 3.04 (1H, dd, J 14.1, 8.9 Hz), 2.66 (3H, s).

Example 23

N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylcarbonylcyclohexylamine



(a) N-Methyl-N-4-methylphenylcarbonylcyclohexylamine

To an ice cold stirred solution of N-methylcylohexylamine (20 ml, 0.15 mol) and triethylamine (22 ml) in dry THF (100 ml) under argon was slowly added p-toluoyl chloride (20 ml, 0.15 mol). A white precipitate formed. The ice bath was removed and the mixture stirred at ambient temperature for 24 h. Ice cold 2N hydrochloric acid (100 ml) was added and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3x100 ml). The combined organics were washed with brine (3x100 ml), dried, filtered and evaporated to give the crude amide, which was crystallised from hexane to give N-methyl-N-4-methylphenylcarbonylcyclohexylamine (30.9 g, 87 %) as a white crystalline solid.

m.p. 70-71°C

i.r. (nujol) 2920, 1640 cm^{-1}

δ_H 7.26 (2H, d, J 8.0 Hz), 7.18 (2H, d, J 8.3 Hz), 4.50, 3.50 (1H, 2br m), 3.08-2.68 (3H, br m), 2.37 (3H, s), 1.93-0.93 (10H, br m).

(b) N-Methyl-N-4-bromomethylphenylcarbonylcyclohexylamine

Utilising the procedure described in Example 1(a) employing N-methyl-N-4-methylphenylcarbonylcyclohexylamine *in lieu* of p-toluenesulphonyl chloride and tetrachloromethane as solvent yielded crude N-methyl-N-4-bromomethylphenylcarbonylcyclohexylamine (67%) as an orange waxy solid.

i.r. (DCM) 2935, 1720 cm^{-1}

δ_H 7.46 (2H, d, J 8.1 Hz), 7.34 (2H, d, J 8.1 Hz), 4.51 (2H, s), 3.78, 3.50 (1H, 2br m), 2.97 (3H, br s), 1.89-0.98 (10H, br m).

(c) N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylcarbonylcyclohexylamine

N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylcarbonylcyclohexylamine by the procedure of Example 4 employing 2-mercaptobenzoxazole *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole and N-methyl-N-4-bromo-methylphenylcarbonylcyclohexylamine *in lieu* of N-4-bromomethylphenyl-sulphonyl-L-leucine ethyl ester.

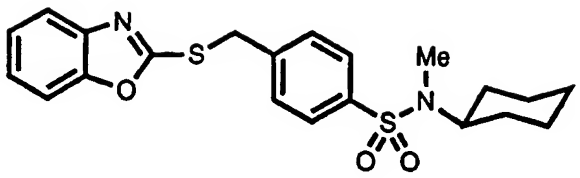
White crystalline solid (36% yield after chromatography (1:2 ethyl acetate/hexane) and crystallisation from ethyl acetate):

Analysis calculated for $C_{22}H_{24}N_2O_2S$
Requires C 69.44 H 6.36 N 7.36
Found C 69.33 H 6.43 N 7.36

δ_H 7.66-7.58 (1H, m), 7.54-7.41 (3H, m), 7.39-7.20 (4H, m), 4.58 (2H, s), 3.51-3.36 (1H, m), 2.95, 2.78 (3H, 2s), 1.90-1.35 (8H, m), 1.20-0.95 (2H, m).

Example 24

N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonylcyclohexylamine



N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonylcyclohexylamine was prepared by the procedure described in Example 23 employing p-tosyl chloride *in lieu* of p-toluyl chloride as starting material.

Pale yellow crystalline solid (65% yield for last step after chromatography (1:2 ethyl acetate/hexane)): m.p. 97°C

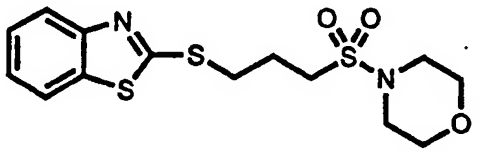
Analysis calculated for $C_{21}H_{24}N_2O_3S_2$
Requires C 60.55 H 5.81 N 6.72
Found C 60.81 H 5.94 N 6.58

i.r. ($CDCl_3$) 2940, 2860, 1600, 1500, 1450, 1335, 1135 cm^{-1}

δ_H 7.76 (2H, d, J 8.3 Hz), 7.66-7.56 (3H, m), 7.48-7.41 (1H, m), 7.37-7.21 (2H, m), 4.59 (2H, s), 3.82-3.68 (1H, m), 2.73 (3H, s), 1.80-1.16 (9H, m), 1.10-0.80 (1H, m).

Example 25

N-3-(Benzoxazol-2-yl)thiopropylsulphonylmorpholine



(a) 3-(Benzoxazol-2-yl)thiopropylsulphonyl chloride

A stirred suspension of sodium 3-(benzoxazol-2-yl)thiopropylsulphononate (10.0 g, 32 mmol) in THF (80 ml) at 0°C was treated with thionyl chloride (14 ml). The reaction mixture was heated at reflux for 3 h, cooled and evaporated under reduced pressure to give crude 3-(benzoxazol-2-yl)thiopropylsulphonyl chloride as a white solid which was used immediately in the next step.

(b) N-3-(Benzoxazol-2-yl)thiopropylsulphonylmorpholine

Crude 3-(benzoxazol-2-yl)thiopropylsulphonyl chloride was suspended in dry THF (80 ml) and treated with an excess (20 ml) of morpholine. The reaction mixture was stirred at room temperature overnight. The material was diluted with saturated ammonium chloride and ethyl acetate, the organic layer washed successively with 2N hydrochloric acid, saturated aqueous sodium hydrogen carbonate, brine, and then dried, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (1:2 ethyl acetate/hexane) to give N-3-(benzoxazol-2-yl)thiopropylsulphonylmorpholine as a white crystalline solid (2.7 g, 24%).

m.p. 107°C

i.r. ($CDCl_3$) 3000-2820, 1425, 1350, 1150, 1110 cm^{-1}

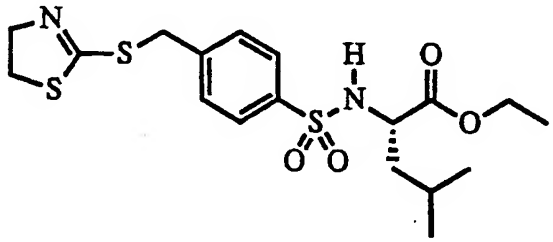
δ_H 7.88-7.82 (1H, m), 7.78-7.73 (1H, m), 7.46-7.37 (1H, m), 7.34-7.25 (1H, m), 3.71 (4H, br t, J 4.5 Hz), 3.51 (2H, t, J 6.9 Hz), 3.25 (4H, br t, J 4.8 Hz), 3.12 (2H, t, J 7.3 Hz), 2.48-2.33 (2H, m);

δ_C 165.34, 152.88, 135.07, 126.02, 124.33, 121.36, 120.92, 66.33, 47.07, 45.62, 31.55, 32.12.

Examples 26-29

The compounds of Examples 26-29 were prepared by the procedure of Example 4 coupling N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester with the appropriate thiol or amine derivative.

26. N-4-(4,5-Dihydrothiazol-2-yl)thiomethylphenylsulphonyl-L-leucine ethyl ester



Colourless oil (14% yield after chromatography (1:1 ethyl acetate/hexane)):

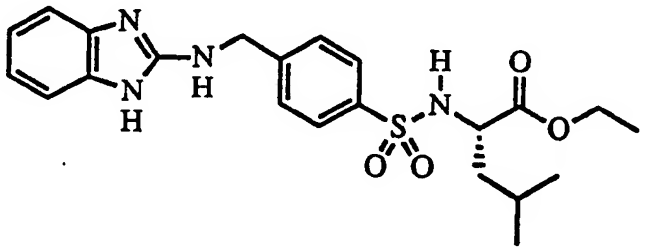
Analysis calculated for $C_{18}H_{26}N_2O_4S_3$

Requires C 50.21 H 6.09 N 6.51
Found C 50.35 H 6.08 N 6.43

i.r. ($CDCl_3$) 1735, 1345, 1165 cm^{-1}

δ_H 7.75 (2H, d, J 8.4 Hz), 7.45 (2H, d, J 8.4 Hz), 5.39 (1H, d, J 10.0 Hz), 4.34 (2H, s), 4.18 (2H, t, J 8.0 Hz), 3.94-3.76 (1H, m), 3.79 (2H, q, J 7.1 Hz), 3.38 (2H, t, J 7.9 Hz), 1.83-1.66 (1H, m), 1.53-1.38 (2H, m), 1.04 (3H, t, J 7.0 Hz), 0.87 (3H, d, J 6.2 Hz), 0.84 (3H, d, J 6.2 Hz).

27. N-4-(N'-Benzimidazol-2-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester



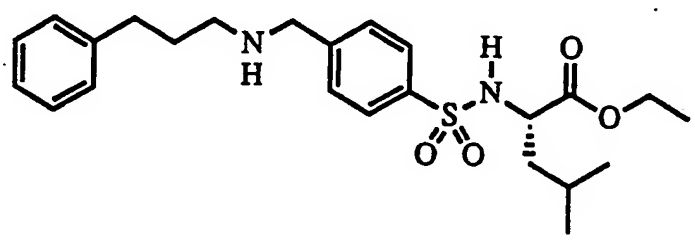
White solid (14% yield after chromatography (5% methanol in DCM): m.p. 185°C

Analysis calculated for $C_{22}H_{28}N_4O_4S.0.4H_2O$
Requires C 58.49 H 6.43 N 12.40
Found C 58.44 H 6.35 N 12.60

i.r. (KBr) 1725 cm^{-1}

δ_H 7.60 (2H, d, J 8.4 Hz), 7.32 (1H, d, J 7.7 Hz), 7.12 (2H, d, J 8.4 Hz), 7.10-6.81 (3H, m), 5.20 (1H, d, J 17.7 Hz), 5.10 (1H, d, J 17.7 Hz), 4.04-3.93 (1H, m), 3.76-3.43 (2H, m), 1.84-1.64 (1H, m), 1.63-1.39 (2H, m), 0.90-0.77 (9H, m).

28. N-4-(N'-3-Phenylpropyl)aminomethylphenylsulphonyl-L-leucine ethyl ester



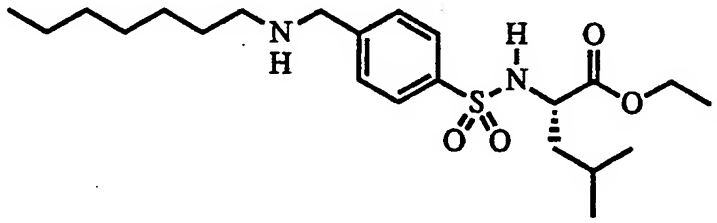
Colourless oil (30% yield after chromatography (5% methanol in DCM)):

i.r. ($CDCl_3$) 1730 cm^{-1}

δ_H 7.78 (2H, d, J 8.3 Hz), 7.43 (2H, d, J 8.3 Hz), 7.34-7.23 (2H, m), 7.22-7.14 (3H, m), 3.96-3.82 (3H, m), 3.83 (2H, s), 2.72-2.60 (4H, m), 1.90-1.70 (3H, m), 1.55-1.43 (2H, m), 1.08 (3H, t, J 7.2 Hz), 0.90 (3H, d, J 6.5 Hz), 0.87 (3H, d, J 6.5 Hz);

δ_C 172.16, 145.87, 141.63, 138.14, 128.33, 128.24, 127.27, 125.34, 61.32, 54.33, 53.09, 48.67, 42.26, 33.45, 31.48, 24.19, 22.62, 21.34, 13.82.

29. N-4-(N'-Heptyl)aminomethylphenylsulphonyl-L-leucine ethyl ester



Colourless oil (55% yield after chromatography (5% methanol in DCM)):

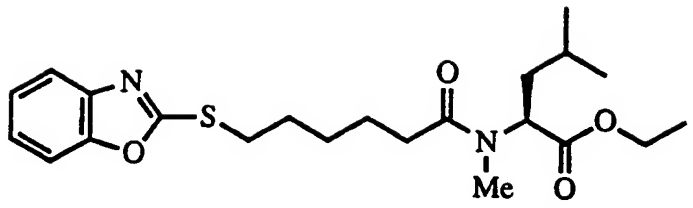
Analysis calculated for $C_{22}H_{38}N_2O_4S.0.4H_2O$
Requires C 60.91 H 9.01 N 6.46
Found C 60.89 H 8.76 N 6.50

i.r. ($CDCl_3$) 1730 cm^{-1}

δ_H 7.76 (2H, d, J 8.3 Hz), 7.42 (2H, d, J 8.3 Hz), 3.94-3.80 (3H, m), 3.82 (2H, s), 2.86 (2H, t, J 7.1 Hz), 1.84-1.69 (1H, m), 1.55-1.40 (4H, m), 1.30-1.20 (8H, m), 1.06 (3H, t, J 7.2 Hz), 0.90-0.80 (9H, m).

Example 30

N-Methyl-N-6-(benzoxazol-2-yl)thiohexanoyl-L-leucine ethyl ester



(a) N-6-Bromo-n-hexanoyl-L-leucine ethyl ester

A stirred suspension of L-leucine ethyl ester hydrochloride (8.38 g, 45 mmol) in dry THF (80 ml) at room temperature was treated with triethylamine (6.3 ml, 45 mmol). The reaction mixture was treated with 6-bromo-n-hexanoyl chloride (6.91 ml, 45 mmol). The reaction mixture was stirred for 4 h at room temperature and then diluted with a mixture of saturated aqueous ammonium chloride and ethyl acetate. The organic layer was separated, washed with saturated aqueous ammonium chloride, dried, filtered and evaporated under reduced pressure to give N-6-bromo-n-hexanoyl-L-leucine ethyl ester (12.1 g, 80%) as an oil which was used for the next step without further purification.

δ_H 5.94 (1H, d, J 8.1 Hz), 4.70-4.55 (1H, m), 4.16 (2H, q, J 7.2 Hz), 3.39 (2H, t, J 6.4 Hz), 2.22 (2H, t, J 7.2 Hz), 1.94-1.80 (2H, m), 1.74-1.39 (7H, m), 1.26 (3H, t, J 7.0 Hz), 0.93 (6H, d, J 5.8 Hz).

(b) N-Methyl-N-6-bromo-n-hexanoyl-L-leucine ethyl ester

Sodium hydride (60% dispersion in oil; 2.0 g, 50 mmol) was added to a stirred solution of N-6-bromo-n-hexanoyl-L-leucine ethyl ester (15.0 g, 45 mmol) in anhydrous THF (150 ml) at 0°C. After the effervesence had ceased methyl iodide (8.4 ml) was added. The reaction mixture was allowed to warm up to room temperature and was stirred overnight. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate, washed with brine, dried filtered and concentrated to give crude N-methyl-N-6-bromo-n-hexanoyl-L-leucine ethyl ester (14.0 g, 89%) as a pale yellow oil which was used directly in the next step.

δ_H 5.31 (1H, dd, J 10.0, 5.7 Hz), 4.20-4.04 (2H, m), 3.39 (2H, t, J 6.7 Hz), 2.89 (2.5H, s), 2.80 (0.5H, s), 2.41-2.28 (2H, m), 1.95-1.56 (6H, m), 1.54-1.36 (3H, m), 1.23 (3H, t, J 7.1 Hz), 0.92 (3H, d, J 6.2 Hz), 0.89 (3H, d, J 6.1 Hz).

(c) N-Methyl-N-6-(benzoxazol-2-yl)thiohexanoyl-L-leucine ethyl ester

A suspension of potassium hydroxide (0.61 g, 10.9 mmol), TDA-1 (4 drops) in dry acetonitrile (150 ml) was stirred for 10 min. at room temperature under argon. 2-Mercaptobenzoxazole (1.65 g, 10.9 mmol) was added and the reaction mixture was heated at 80°C for 2 h and cooled to 40°C. A solution of N-methyl-N-6-bromo-n-hexanoyl-L-leucine ethyl ester (3.7 g, 10.9 mmol) in dry acetonitrile (50 ml) was added and the reaction mixture stirred at 80°C overnight and cooled to room temperature. the solvent was removed and the residue taken up in ethyl acetate, washed with brine, dried, filtered and concentrated. Column chromatography (30% ethyl acetate in hexane) gave N-methyl-N-6-(benzoxazol-2-yl)thiohexanoyl-L-leucine ethyl ester (1.5 g, 33%) as a yellow oil.

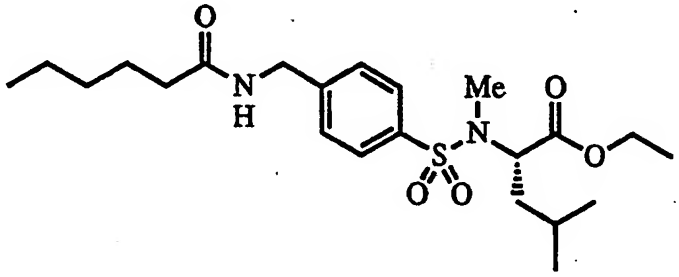
Analysis calculated for $C_{22}H_{32}N_2O_4S$
Requires C 62.83 H 7.67 N 6.66
Found C 62.87 H 7.69 N 6.59

i.r. ($CDCl_3$) 2215, 1730, 1630, 1445, 1400, 1240, 1130 cm^{-1}

δ_H 7.58-7.51 (1H, m), 7.38-7.32 (1H, m), 7.27-7.12 (2H, m), 5.29 (1H, dd, J 10.1, 5.7 Hz), 4.16-4.03 (2H, m), 3.26 (2H, t, J 7.3 Hz), 2.85 (3H, s), 2.36-2.30 (2H, m), 1.88-1.33 (9H, m), 1.19 (3H, t, J 7.2 Hz), 0.89 (3H, d, J 6.7 Hz), 0.87 (3H, d, J 6.5 Hz).

Example 31

N-Methyl-N-4-(N'-hexanoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester



A solution of N-methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester hydrochloride (6.5 g, 0.017 mol) and triethylamine (2.4 ml) in dry DCM was added to a stirred solution of pentafluorophenylhexanoate (4.86 g, mmol) in dry DCM (250 ml). The mixture was stirred overnight at room temperature and the solvent removed under reduced pressure. The residue was partitioned between water and ethyl acetate. The organic layer was separated and dried, filtered and

evaporated. Chromatography (3% methanol in DCM) gave N-methyl-N-4-(N'-hexanoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester (0.64 g, 8%) as a colourless oil.

i.r. ($CDCl_3$) 1735, 1665, 1510, 1340, 1150 cm^{-1}

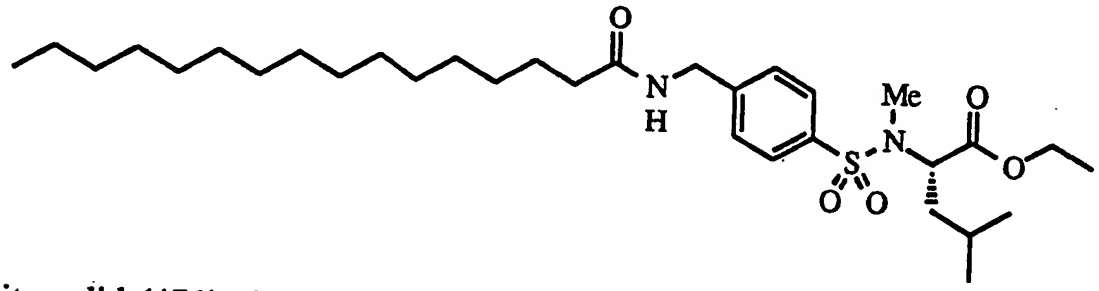
δ_H 7.54 (2H, d, J 8.4 Hz), 7.25 (2H, d, J 8.5 Hz), 6.79 (1H, t, J 7.0 Hz), 4.61-4.52 (1H, m), 4.38 (2H, d, J 6.0 Hz), 3.88-3.74 (2H, m), 2.74 (3H, s), 2.18 (2H, t, J 7.6 Hz), 1.67-1.47 (5H, m), 1.32-1.17 (4H, m), 0.99 (3H, t, J 7.1 Hz), 0.94-0.78 (9H, m);

δ_C 173.57, 170.62, 143.86, 137.22, 127.40, 127.12, 60.73, 56.93, 42.28, 37.81, 36.09, 31.14, 29.45, 25.16, 24.12, 22.71, 22.06, 20.84.

Examples 32-35

The compounds of Examples 32-35 were prepared by the procedure of Example 31 coupling N-methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester with the appropriate carboxylic acid chloride or activated ester.

32. N-Methyl-N-4-(N'-hexadecanoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester



White solid (47% yield after chromatography (1:4 ethyl acetate/hexane)): m.p. 62°C

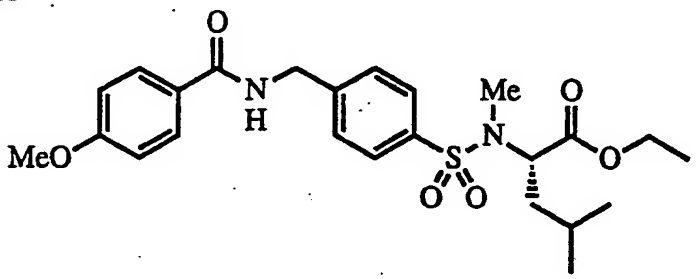
Analysis calculated for $C_{32}H_{56}N_2O_5S$
Requires C 66.17 H 9.72 N 4.82
Found C 66.03 H 9.60 N 4.90

i.r. ($CDCl_3$) 1735, 1665, 1340, 1150 cm^{-1}

δ_H 7.53 (2H, d, J 8.3 Hz), 7.23 (2H, d, J 8.2 Hz), 6.81 (1H, t, J 5.9 Hz), 4.60-4.50 (1H, m), 4.44-4.26 (2H, m), 3.90-3.62 (2H, m), 2.73 (3H, s), 2.16 (2H, t, J

7.3 Hz), 1.66-1.48 (3H, m), 1.30-1.10 (26H, m), 0.98 (3H, t, J 7.1 Hz), 0.93-0.82 (6H, m), 0.81 (3H, t, J 6.2 Hz).

33. N-Methyl-N-4-(N'-4-methoxybenzoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester



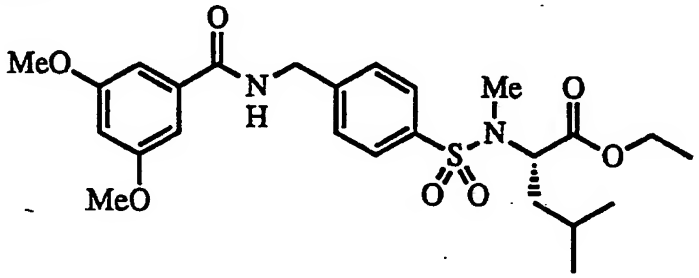
Colourless oil (53% yield after chromatography (ethyl acetate)):

i.r. ($CDCl_3$) 1730, 1655 cm^{-1}

δ_H 7.77 (2H, d, J 8.8 Hz), 7.59 (2H, d, J 8.3 Hz), 7.33 (2H, d, J 8.3 Hz), 7.30-7.22 (1H, m), 6.85 (2H, d, J 8.8 Hz), 4.65-4.52 (3H, m), 3.90-3.70 (2H, m), 3.80 (3H, s), 2.77 (3H, s), 1.70-1.50 (3H, m), 0.99 (3H, t, J 7.2 Hz), 0.84 (3H, d, J 6.6 Hz), 0.82 (3H, d, J 6.4 Hz);

δ_C 170.78, 167.01, 162.18, 143.97, 137.43, 128.81, 127.62, 127.33, 126.04, 113.57, 60.87, 57.06, 55.24, 42.92, 37.97, 29.61, 24.25, 22.87, 21.25.

34. N-Methyl-N-4-(N'-3,5-dimethoxybenzoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester



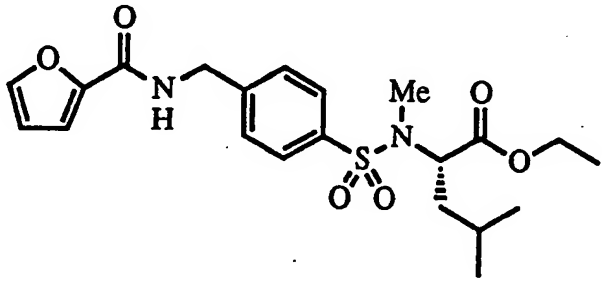
Colourless oil (40% yield after chromatography (1:1 ethyl acetate/hexane)):

i.r. ($CDCl_3$) 1725, 1655, 1590, 1345, 1150 cm^{-1}

δ_H 7.59 (2H, d, J 8.2 Hz), 7.33 (2H, d, J 8.3 Hz), 6.94 (2H, d, J 2.2 Hz), 6.55 (1H, t, J 2.2 Hz), 4.67-4.57 (3H, m), 3.93-3.70 (3H, m), 3.77 (6H, s), 2.77 (3H, s), 1.62-1.50 (3H, m), 1.01 (3H, t, J 7.2 Hz), 0.96-0.88 (6H, m);

δ_C 170.84, 167.31, 160.77, 143.62, 137.57, 135.97, 127.64, 127.39, 104.92, 103.63, 60.92, 57.09, 55.40, 43.07, 37.80, 29.63, 24.28, 22.91, 21.03, 13.80.

35. N-Methyl-N-4-(N'-furan-2-ylcarbonyl)aminomethylphenylsulphonyl-L-leucine ethyl ester



Colourless oil (62% yield after chromatography (1:1 ethyl acetate/hexane)):

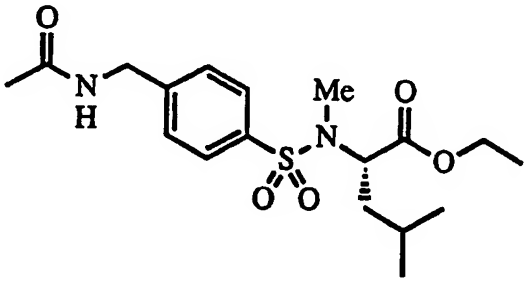
i.r. ($CDCl_3$) 1730, 1660, 1340 cm^{-1}

δ_H 7.59 (2H, d, J 8.4 Hz), 7.38-7.28 (4H, m), 7.02 (1H, d, J 3.3 Hz), 6.40 (1H, dd, J 3.3, 1.9 Hz), 4.60-4.50 (3H, m), 3.89-3.66 (2H, m), 2.74 (3H, s), 1.60-1.45 (3H, m), 0.94 (3H, t, J 7.2 Hz), 0.87 (3H, d, J 6.0 Hz), 0.86 (3H, d, J 6.1 Hz);

δ_C 170.66, 158.26, 147.34, 143.99, 143.36, 137.54, 127.64, 127.26, 114.19, 111.84, 60.72, 59.93, 42.02, 37.84, 29.48, 24.10, 22.72, 20.84, 13.58.

Example 36

N-Methyl-N-4-(N'-acetyl)aminomethylphenylsulphonyl-L-leucine ethyl ester



N-Methyl-N-4-(N'-acetyl)aminomethylphenylsulphonyl-L-leucine ethyl ester was prepared by the method of Example 8 employing N-methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester as starting material.

Colourless oil (57% yield after chromatography (ethyl acetate)):

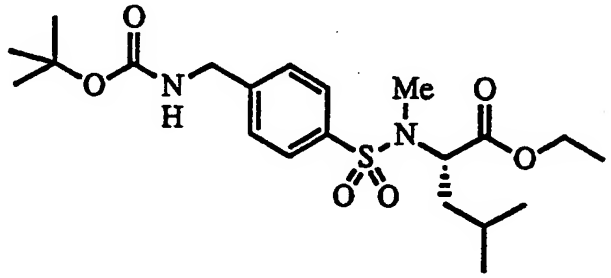
i.r. ($CDCl_3$) 1735, 1670, 1345, 1170 cm^{-1}

δ_H 7.60 (2H, d, J 8.4 Hz), 7.29 (2H, d, J 8.3 Hz), 6.65 (1H, br t, J 5.4 Hz), 4.64-4.55 (1H, m), 4.46-4.36 (2H, m), 3.94-3.74 (2H, m), 2.77 (3H, s), 1.99 (3H, s), 1.65-1.50 (3H, m), 1.03 (3H, t, J 7.2 Hz), 0.92 (3H, d, J 6.1 Hz), 0.91 (3H, d, J 6.1 Hz);

δ_C 170.84, 170.31, 143.68, 137.65, 127.68, 127.41, 60.91, 57.12, 42.70, 38.03, 29.64, 24.31, 22.91, 21.06, 20.90, 13.83.

Example 37

N-Methyl-N-4-(N'-t-butyloxycarbonyl)aminomethylphenylsulphonyl-L-leucine ethyl ester



Triethylamine (1.12 ml, 8.07 mmol) was added dropwise to a stirred mixture of N-methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester hydrochloride (2.50 g, 6.46 mmol) and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (1.91 g, 7.75 mmol) in dioxane (15 ml) and water (15 ml) at room temperature. The dioxane was removed under reduced pressure and dichloromethane added to the residue. The mixture was washed with 1N hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine. The organics were dried, filtered and evaporated. Chromatography (1:4 ethyl acetate/hexane) gave N-methyl-N-4-(N'-t-butyloxycarbonyl)amino-methylphenylsulphonyl-L-leucine ethyl ester (2.38 g, 83%) as a colourless oil.

Analysis calculated for $C_{21}H_{34}N_2O_6S$
Requires C 56.99 H 7.74 N 6.33
Found C 57.09 H 7.69 N 6.49

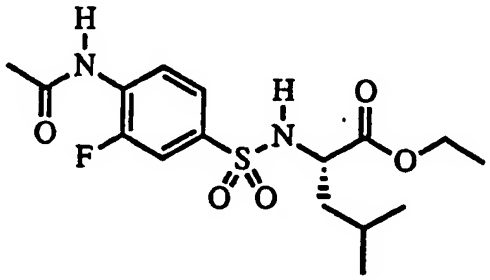
i.r. (neat) 3600-3200, 2960, 2860, 1750-1650, 1520, 1360, 1170 cm^{-1}

δ_H 7.75 (2H, d, J 8.2 Hz), 7.38 (2H, d, J 8.1 Hz), 5.02 (1H, br s), 4.67 (1H, t, J 7.5 Hz), 4.35 (2H, d, J 5.9 Hz), 3.89 (2H, dd, J 6.9, 5.1 Hz), 2.82 (3H, s), 1.61 (3H, br m), 1.45 (9H, s), 1.07 (3H, t, J 7.1 Hz), 0.96 (6H, m).

Examples 38-57

The compounds of Examples 38-57 were prepared by the procedure of Example 1 Step (b) involving the condensation of the appropriate sulphonyl chloride derivative or carbonyl chloride derivative with the appropriate amine derivative.

38. N-4-(N'-Acetyl)amino-3-fluorophenylsulphonyl-L-leucine ethyl ester



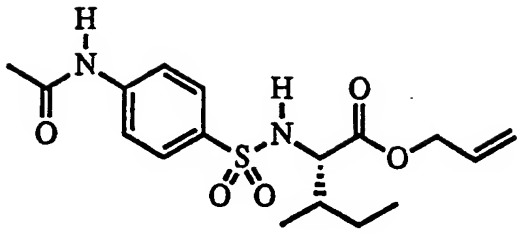
White crystalline solid (55% yield after chromatography (2:1 ethyl acetate/hexane)): m.p. 100°C

i.r. ($CDCl_3$) 1720, 1340, 1150 cm^{-1}

δ_H 8.76-8.70 (0.5H, m), 8.48-8.38 (0.5H, m), 8.25-8.15 (1H, m), 7.55-7.45 (1.5H, m), 7.10 (0.5H, dd, J 10.3, 8.7 Hz), 5.80-5.70 (1H, m), 3.96-3.80 (3H, m), 2.21 (1.5H, s), 2.17 (1.5H, s), 1.80-1.62 (1H, m), 1.50-1.38 (2H, m), 1.07 (1.5H, t, J 7.0 Hz), 1.03 (1.5H, t, J 7.0 Hz), 0.88-0.77 (6H, m).

δ_C 171.99, 171.92, 169.22, 168.91, 156.41, 152.96, 152.40, 149.01, 136.23, 134.63, 134.53, 130.71, 130.55, 127.13, 126.95, 123.43, 123.30, 121.17, 121.07, 115.37, 115.03, 114.09, 113.72, 61.38, 61.26, 60.22, 54.31, 41.88, 24.32, 24.07, 22.43, 21.17, 20.78, 13.92, 13.63.

39. N-4-(N'-Acetyl)aminophenylsulphonyl-L-isoleucine allyl ester



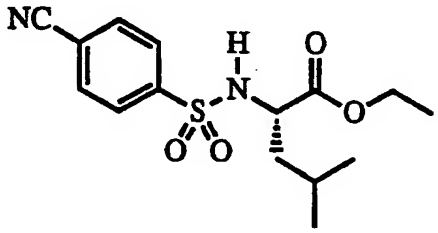
White crystalline solid (70% yield after crystallisation from ethyl acetate/hexane): m.p. 110°C

Analysis calculated for $C_{17}H_{24}N_2O_5S.0.2H_2O$
Requires C 54.88 H 6.61 N 7.53
Found C 54.82 H 6.54 N 7.43

i.r. ($CDCl_3$) 1735, 1705, 1510, 1345, 1160 cm^{-1}

δ_H 8.20 (1H, s), 7.69 (2H, d, J 8.9 Hz), 7.63 (2H, d, J 9.0 Hz), 5.80-5.60 (1H, m), 5.45 (1H, d, J 9.9 Hz), 5.25-5.12 (2H, m), 4.42-4.26 (2H, m), 3.79 (1H, dd, J 9.9, 5.4 Hz), 2.19 (3H, s), 1.86-1.70 (1H, m), 1.50-1.32 (1H, m), 1.21-1.05 (1H, m), 0.94-0.80 (6H, m).

40. N-4-Cyanophenylsulphonyl-L-leucine ethyl ester



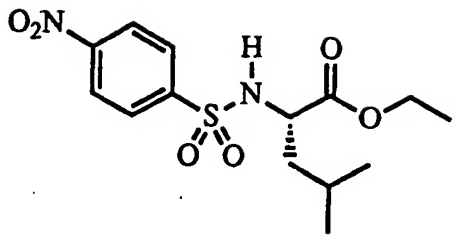
Colourless oil (75% yield after chromatography (1:3 ethyl acetate/hexane)):

i.r. ($CDCl_3$) 2210, 1730, 1345, 1160 cm^{-1}

δ_H 7.93 (2H, d, J 8.6 Hz), 7.74 (2H, d, J 8.6 Hz), 5.88 (1H, d, J 9.9 Hz), 3.96-3.82 (1H, m), 3.85 (2H, q, J 7.1 Hz), 1.77-1.60 (1H, m), 1.50-1.40 (2H, m), 1.04 (3H, t, J 7.0 Hz), 0.83 (3H, d, J 6.9 Hz), 0.80 (3H, d, J 6.8 Hz).

δ_C 170.42, 142.94, 131.35, 126.43, 115.86, 114.79, 60.16, 58.94, 53.12, 40.51, 28.83, 24.10, 21.20, 19.82, 12.45.

41. N-4-Nitrophenylsulphonyl-L-leucine ethyl ester



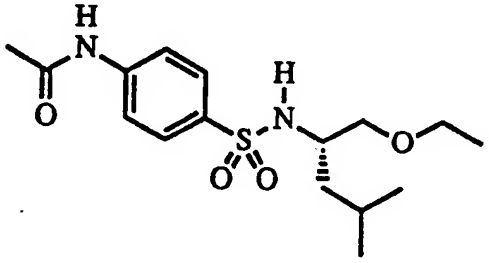
White crystalline solid (60% yield after chromatography (1:3 ethyl acetate/hexane)): m.p. 86-87°C

Analysis calculated for $C_{14}H_{20}N_2O_6S$
Requires C 48.83 H 5.85 N 8.13
Found C 48.78 H 5.86 N 8.13

i.r. ($CDCl_3$) 1740, 1350, 1170 cm^{-1}

δ_H 8.33 (2H, d, J 8.8 Hz), 8.04 (2H, d, J 8.8 Hz), 5.54 (1H, d, J 9.9 Hz), 4.05-3.92 (1H, m), 3.92 (2H, q, J 7.4 Hz), 1.83-1.69 (1H, m), 1.60-1.46 (2H, m), 1.10 (3H, t, J 7.1 Hz), 0.90 (3H, d, J 6.7 Hz), 0.89 (3H, d, J 6.5 Hz).

42. N-4-(N'-Acetyl)aminophenylsulphonyl-L-leucinyl ethyl ether



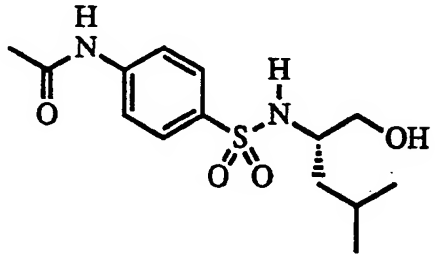
White crystalline solid (60% yield after chromatography (ethyl acetate)): m.p. 121°C

Analysis calculated for $C_{16}H_{26}N_2O_4S$
Requires C 56.12 H 7.65 N 8.18
Found C 56.14 H 7.67 N 8.18

i.r. ($CDCl_3$) 1700, 1590, 1510, 1150 cm^{-1}

δ_H 8.51 (1H, s), 7.75 (2H, d, J 8.8 Hz), 7.66 (2H, d, J 8.9 Hz), 5.10 (1H, d, J 8.4 Hz), 3.43-3.08 (5H, m), 2.17 (3H, s), 1.67-1.49 (1H, m), 1.48-1.20 (2H, m), 1.05 (3H, t, J 6.9 Hz), 0.80 (3H, d, J 6.6 Hz), 0.74 (3H, d, J 6.5 Hz).

43. N-4-(N'-Acetyl)aminophenylsulphonyl-L-leucinol



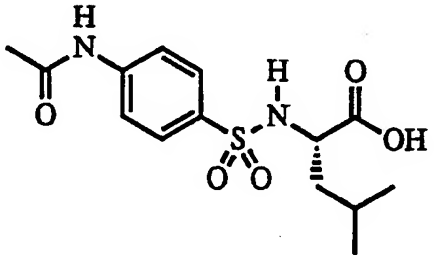
White crystalline solid (35% yield after crystallisation from ethyl acetate): m.p. 168°C

Analysis calculated for $C_{14}H_{22}N_2O_4S$
Requires C 53.48 H 7.05 N 8.91
Found C 53.12 H 6.96 N 8.81

i.r. (KBr) 1680, 1590, 1530, 1150 cm^{-1}

δ_H (D_6-DMSO) 10.28 (1H, s), 7.80-7.63 (4H, m), 7.29 (1H, d, J 7.2 Hz), 4.61-4.46 (1H, m), 3.30-3.18 (1H, m), 3.16-3.00 (2H, m), 2.08 (3H, s), 1.53-1.40 (1H, m), 1.38-1.20 (1H, m), 1.20-1.05 (1H, m), 0.73 (3H, d, J 6.5 Hz), 0.56 (3H, d, J 6.4 Hz).

44. N-4-(N'-Acetyl)aminophenylsulphonyl-L-leucine



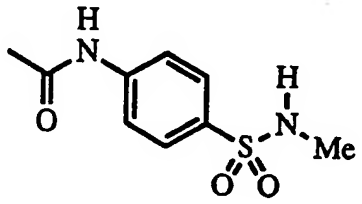
White crystalline solid (crystallised from DIPE/ethyl acetate/hexane): m.p. 223°C

Analysis calculated for $C_{14}H_{20}N_2O_5S.0.3H_2O$
Requires C 50.38 H 6.22 N 8.39
Found C 50.35 H 6.18 N 8.28

i.r. (KBr) 3600-2700, 1725, 1675, 1390, 1320, 1130 cm^{-1}

δ_H (D_6-DMSO) 12.51 (1H, br s), 10.26 (1H, s), 7.95 (1H, d, J 8.9 Hz), 7.89-7.60 (4H, m), 3.70-3.54 (1H, m), 2.07 (3H, s), 1.67-1.45 (1H, m), 1.46-1.26 (2H, m), 0.79 (3H, d, J 6.6 Hz), 0.69 (3H, d, J 6.5 Hz).

45. N-Methyl 4-(N'-Acetyl)aminophenylsulphonamide



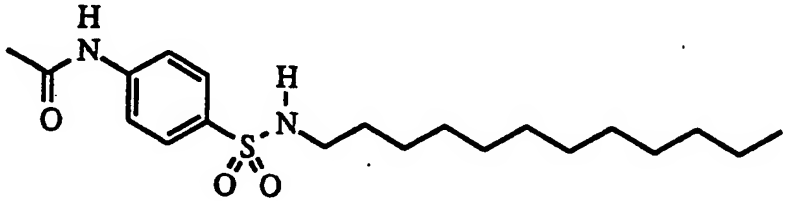
White crystalline solid (50% yield after crystallisation from DIPE/methanol/hexane): m.p. 185°C

Analysis calculated for $C_9H_{12}N_2O_3S$
Requires C 47.36 H 5.30 N 12.27
Found C 47.29 H 5.37 N 12.22

i.r. (KBr) 1690, 1600, 1155 cm^{-1}

δ_H (D_6-DMSO) 7.65 (4H, s), 2.39 (3H, s), 2.04 (3H, s).

46. N-Dodecyl 4-(N'-Acetyl)aminophenylsulphonamide



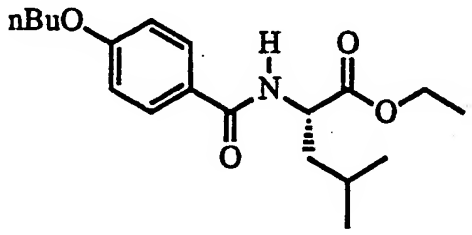
White crystalline solid (53% yield after crystallisation from DIPE/methanol/hexane): m.p. 122°C

Analysis calculated for $C_{20}H_{34}N_2O_3S$
Requires C 62.79 H 8.96 N 7.32
Found C 62.88 H 9.02 N 7.24

i.r. (KBr) 1685, 1590, 1530, 1320, 1150 cm^{-1}

δ_H 8.30 (1H, s), 7.71 (2H, d, J 8.9 Hz), 7.62 (2H, d, J 8.8 Hz), 5.01 (1H, t, J 6.1 Hz), 2.89 (2H, q, J 6.8 Hz), 2.19 (3H, s), 1.52-1.39 (2H, m), 1.31-1.13 (18H, m), 0.87 (3H, t, J 6.3 Hz).

47. N-4-n-Butoxyphenylcarbonyl-L-leucine ethyl ester



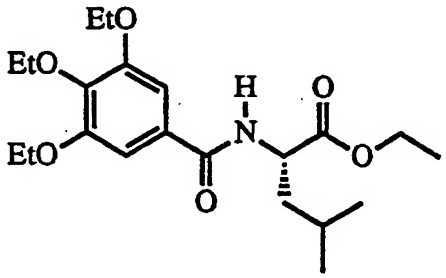
Colourless oil (38% yield after chromatography (1:4 ethyl acetate/hexane)):

i.r. ($CDCl_3$) 1745, 1660, 1610 cm^{-1}

δ_H 7.72 (2H, d, J 9.4 Hz), 6.84 (2H, d, J 9.3 Hz), 6.74 (1H, d, J 8.3 Hz), 4.87-4.76 (1H, m), 4.19 (2H, q, J 7.1 Hz), 3.94 (2H, t, J 6.6 Hz), 1.80-1.56 (5H, m), 1.53-1.38 (2H, m), 1.25 (3H, t, J 7.0 Hz), 1.00-0.88 (9H, m);

δ_C 173.44, 166.55, 161.75, 128.74, 125.81, 113.99, 67.67, 61.17, 50.98, 41.65, 31.01, 24.84, 22.74, 21.90, 19.05, 14.02, 13.67.

48. N-3,4,5-Triethoxyphenylcarbonyl-L-leucine ethyl ester



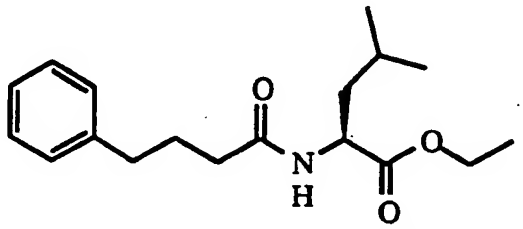
White crystalline solid (45% yield after chromatography (1:2 ethyl acetate/hexane)): m.p. 109°C

Analysis calculated for $C_{21}H_{33}NO_6.0.3H_2O$
Requires C 62.92 H 8.45 N 3.49
Found C 62.90 H 8.25 N 3.52

i.r. ($CDCl_3$) 1735, 1660, 1585 cm^{-1}

δ_H 7.00 (2H, s), 6.55 (1H, d, J 8.2 Hz), 4.88-4.77 (1H, m), 4.23 (2H, q, J 7.2 Hz), 4.15-4.03 (6H, m), 1.80-1.60 (3H, m), 1.48-1.23 (12H, m), 1.04-0.92 (6H, m).

49. N-4-Phenylbutanoyl-L-leucine ethyl ester



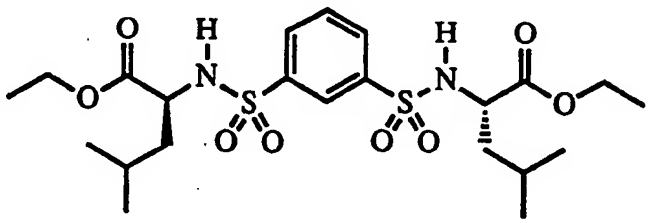
Colourless oil (63% yield after chromatography (1:2 ethyl acetate/hexane)):

i.r. ($CDCl_3$) 1735, 1665 cm^{-1}

δ_H 7.34-7.21 (2H, m), 7.20-7.12 (3H, m), 6.12 (1H, d, J 8.3 Hz), 4.70-4.56 (1H, m), 4.16 (2H, q, J 7.2 Hz), 2.64 (2H, t, J 7.4 Hz), 2.22 (2H, t, J 7.3 Hz), 2.01-1.89 (2H, m), 1.73-1.48 (3H, m), 1.26 (3H, t, J 7.0 Hz), 0.94 (3H, d, J 6.1 Hz), 0.93 (3H, d, J 6.3 Hz);

δ_C 173.13, 172.38, 141.32, 128.31, 128.18, 125.74, 61.06, 50.45, 41.49, 35.42, 34.94, 26.90, 24.71, 22.64, 21.78, 13.96.

50. 1,3-Di(N-sulphonyl-L-leucine ethyl ester)benzene



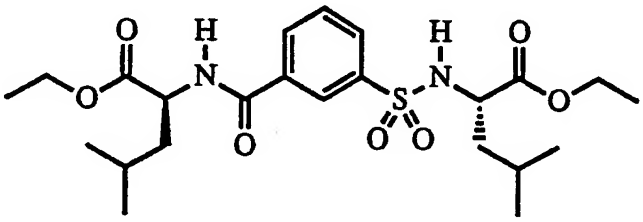
Colourless oil (50% yield after chromatography (1:2 ethyl acetate/hexane)):

i.r. ($CDCl_3$) 1735, 1350, 1170 cm^{-1}

δ_H 8.27-8.24 (1H, m), 8.00-7.93 (2H, m), 7.58 (1H, dd, J 7.8, 7.8 Hz), 6.02 (2H, d, J 9.9 Hz), 4.00-3.78 (2H, m), 3.79 (4H, q, J 7.1 Hz), 1.70-1.60 (2H, m), 1.50-1.38 (4H, m), 1.00 (6H, t, J 7.1 Hz), 0.81 (6H, d, J 6.6 Hz), 0.78 (6H, d, J 6.4 Hz);

δ_C 171.61, 141.32, 133.34, 130.67, 125.52, 61.35, 54.31, 41.64, 24.00, 22.38, 21.05, 13.52.

51. N-3-(O-Ethyl-L-leucinecarboxy)phenylsulphonyl-L-leucine ethyl ester



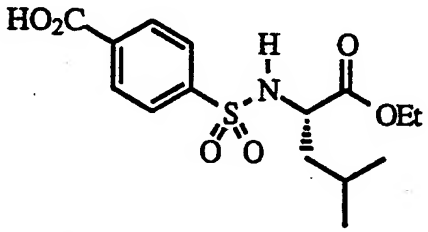
Colourless oil (44% yield after chromatography (1:2 ethyl acetate/hexane)):

Analysis calculated for $C_{23}H_{36}N_2O_7S.0.9H_2O$
Requires C 55.16 H 7.61 N 5.59
Found C 55.25 H 7.21 N 5.55

i.r. ($CDCl_3$) 1725, 1660, 1340, 1170 cm^{-1}

δ_H 8.25-8.22 (1H, m), 8.04-7.91 (2H, m), 7.52 (1H, t, J 7.8 Hz), 7.09 (1H, d, J 8.2 Hz), 5.66 (1H, d, J 9.9 Hz), 4.86-4.73 (1H, m), 4.20 (2H, q, J 7.2 Hz), 4.01-3.86 (1H, m), 3.85 (2H, q, J 7.0 Hz), 1.80-1.61 (4H, m), 1.55-1.40 (2H, m), 1.27 (3H, t, J 7.0 Hz), 1.04 (3H, t, J 7.0 Hz), 1.00-0.89 (6H, m), 0.87 (3H, d, J 5.7 Hz), 0.84 (3H, d, J 5.7 Hz).

52. N-4-(Hydroxycarbonyl)phenylsulphonyl-L-leucine ethyl ester



Off-white crystalline solid (4% yield after crystallisation (DIPE/chloroform)):

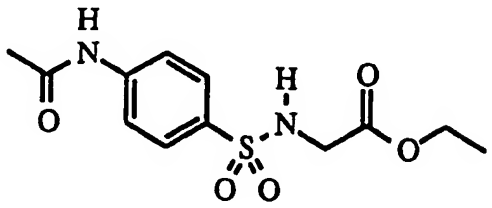
Analysis calculated for $C_{15}H_{21}NO_6S$
Requires C 52.47 H 6.16 N 4.08
Found C 52.10 H 6.05 N 3.99

i.r. ($CDCl_3$) 3400-2400, 1735, 1700, 1350, 1165 cm^{-1}

δ_H 9.70-9.25 (1H, br s), 8.21 (2H, d, J 8.4 Hz), 7.96 (2H, d, J 8.4 Hz), 5.60 (1H, d, J 9.9 Hz), 4.07-3.86 (1H, m), 3.91 (2H, q, J 7.1 Hz), 1.80-1.70 (1H, m), 1.60-

1.45 (2H, m), 1.11 (3H, t, J 7.0 Hz), 0.91 (3H, d, J 6.6 Hz), 0.89 (3H, d, J 6.5 Hz).

53. N-4-(N'-Acetyl)aminophenylsulphonylglycine ethyl ester



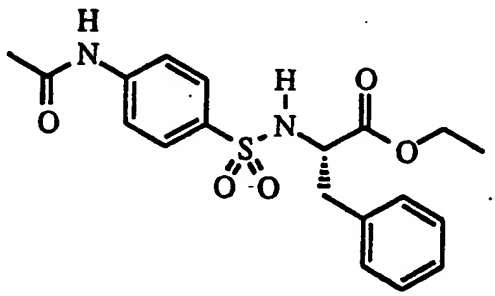
White crystalline solid (52% yield after crystallisation (DIPE/methanol/hexane)): m.p. 130°C

Analysis calculated for $C_{12}H_{16}N_2O_5S$
Requires C 47.99 H 5.37 N 9.33
Found C 48.05 H 5.36 N 9.34

i.r. (KBr) 1725, 1670, 1595, 1350, 1160 cm^{-1}

δ_H (CD_3OD) 7.78-7.65 (4H, m), 3.96 (2H, q, J 7.2 Hz), 3.69 (2H, s), 2.11 (3H, s), 1.10 (3H, t, J 7.2 Hz).

54. N-4-(N'-Acetyl)aminophenylsulphonyl-L-phenylalanine ethyl ester



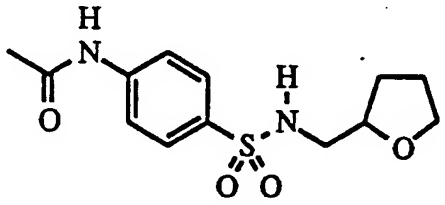
White crystalline solid (60% yield after crystallisation (DIPE/methanol/hexane)): m.p. 145°C

Analysis calculated for $C_{19}H_{22}N_2O_5S$
Requires C 58.45 H 5.68 N 7.17
Found C 58.47 H 5.69 N 7.21

i.r. (KBr) 1735, 1705, 1345, 1155 cm^{-1}

δ_H 7.82 (1H, s), 7.65 (2H, d, J 8.8 Hz), 7.57 (2H, d, J 8.8 Hz), 7.30-7.18 (3H, m), 7.13-7.03 (2H, m), 5.26 (1H, d, J 9.1 Hz), 4.22-4.10 (1H, m), 3.94 (2H, q, J 6.8 Hz), 3.03 (2H, d, J 6.1 Hz), 2.19 (3H, s), 1.08 (3H, t, J 6.7 Hz).

55. N-4-(N'-Acetyl)aminophenylsulphonyltetrahydrofurfurylamine



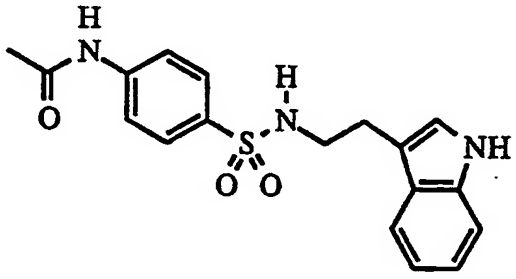
White crystalline solid (50% yield after crystallisation (DIPE/methanol/hexane)): m.p. 129°C

Analysis calculated for $C_{13}H_{18}N_2O_4S$
Requires C 52.33 H 6.08 N 9.39
Found C 52.51 H 6.13 N 9.34

i.r. (KBr) 1690, 1610, 1590, 1530, 1330, 1150 cm^{-1}

δ_H (CD_3OD) 7.80-7.66 (4H, m), 3.91-3.56 (3H, m), 2.88 (1H, dd, J 13.2, 5.2 Hz), 2.81 (1H, dd, J 13.1, 6.0 Hz), 2.11 (3H, s), 2.00-1.72 (3H, m), 1.64 -1.50 (1H, m).

56. N-4-(N'-Acetyl)aminophenylsulphonyltryptamine



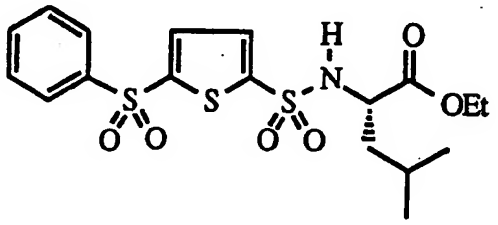
Off-white crystalline solid (50% yield after crystallisation (DIPE/methanol/hexane)): m.p. 152°C

Analysis calculated for $C_{18}H_{19}N_3O_3S$
Requires C 60.49 H 5.36 N 11.76
Found C 60.59 H 5.40 N 11.79

i.r. (KBr) 1690, 1605, 1595, 1535, 1325, 1150 cm^{-1}

δ_H (CD_3OD) 7.90-7.59 (4H, m), 7.32 (1H, dd, J 8.8, 1.0 Hz), 7.23 (1H, dd, J 8.2, 1.0 Hz), 7.00 (1H, dt, J 7.2, 1.2 Hz), 6.95-6.83 (2H, m), 3.10 (2H, t, J 7.1 Hz), 2.81 (2H, t, J 7.6 Hz), 2.09 (3H, s).

57. 5-(Phenylsulphonyl)thien-2-ylsulphonyl-L-leucine ethyl ester



White crystalline solid (68% yield after chromatography (1:1 ethyl acetate/hexane)): m.p. 96°C

Analysis calculated for $C_{18}H_{23}NO_6S_3$
Requires C 48.52 H 5.20 N 3.14
Found C 48.65 H 5.16 N 3.11

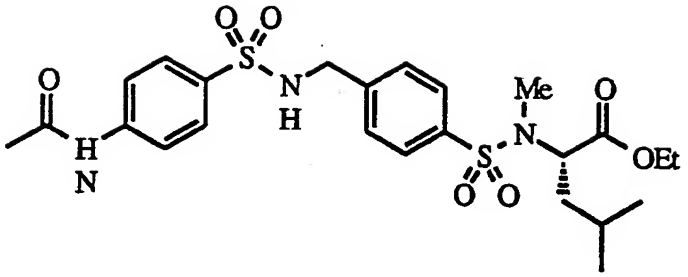
i.r. ($CDCl_3$) 3340, 3100-2800, 1735, 1350, 1155 cm^{-1}

δ_H 7.93 (2H, d, J 8.5 Hz), 7.64-7.43 (5H, m), 5.93 (1H, d, J 9.9 Hz), 4.05-3.88 (1H, m), 3.79 (2H, q, J 7.1 Hz), 1.80-1.60 (1H, m), 1.55-1.40 (2H, m), 1.00 (3H, t, J 7.1 Hz), 0.81 (3H, d, J 7.2 Hz), 0.79 (3H, d, J 6.9 Hz).

Examples 58 and 59

The compounds of Examples 58 and 59 were prepared by the procedure of Example 1 Step (b) involving the condensation of the appropriate sulphonyl chloride derivative or carbonyl chloride derivative with N-methyl-N-4-aminomethylphenylsulphonyl-L-leucine ethyl ester hydrochloride.

58. N-Methyl-N-4-(N'-4-(N''-acetyl)aminophenylsulphonyl)aminomethyl-phenylsulphonyl-L-leucine ethyl ester



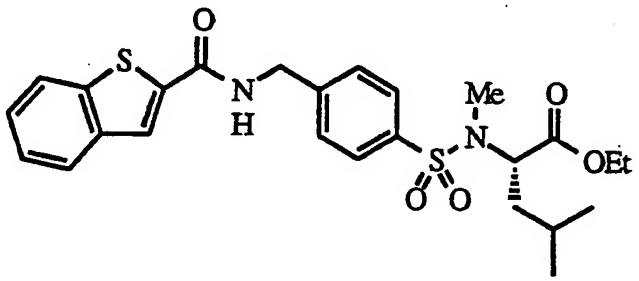
White crystalline solid (54% yield after crystallisation (DIPE/methanol/hexane)): m.p. 117°C

Analysis calculated for $C_{24}H_{33}N_3O_7S_2$
Requires C 53.42 H 6.16 N 7.79
Found C 53.71 H 6.17 N 7.80

i.r. (KBr) 1745, 1680, 1590, 1150 cm^{-1}

δ_H (CD_3OD) 7.77-7.62 (4H, m), 7.63 (2H, d, J 8.5 Hz), 7.38 (2H, d, J 8.4 Hz), 4.60-4.50 (1H, m), 4.10 (2H, s), 3.92-3.70 (2H, m), 2.77 (3H, s), 2.12 (3H, s), 1.65-1.50 (3H, m), 1.01 (3H, t, J 7.2 Hz), 0.90-0.84 (6H, m).

59. N-Methyl-N-4-(N'-2-benzo[b]thienylcarbonyl)aminomethylphenylsulphonyl-L-leucine ethyl ester



White solid foam (purified by chromatography (1:1 ethyl acetate/hexane)): m.p. 45°C

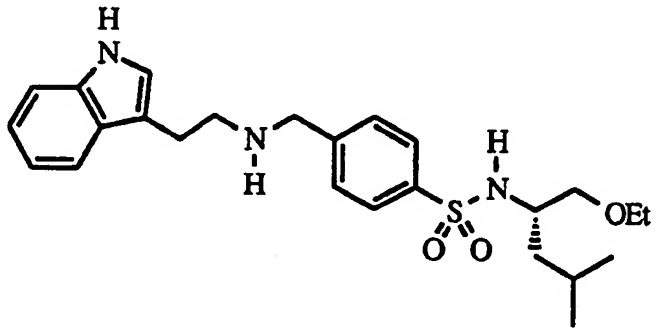
Analysis calculated for $C_{25}H_{30}N_2O_5S_2$
Requires C 59.74 H 6.02 N 5.57
Found C 59.51 H 6.06 N 5.47

i.r. ($CDCl_3$) 1735, 1660, 1345, 1155 cm^{-1}

δ_H 7.89 (1H, s), 7.88-7.75 (2H, m), 7.61 (2H, d, J 8.3 Hz), 7.47-7.25 (5H, m), 4.70-4.60 (3H, m), 3.95-3.78 (2H, m), 2.81 (3H, s), 1.70-1.54 (3H, m), 1.02 (3H, t, J 7.1 Hz), 0.97-0.90 (6H, m).

Example 60

N-4-(N'-2-Indolol-3-ylethyl)aminomethylphenylsulphonyl-L-leucinyl ethyl ether



N-4-(N'-2-Indolol-3-ylethyl)aminomethylphenylsulphonyl-L-leucinyl ethyl ether was prepared by the procedure of Example 4 employing 2-indolol-3-ylethylamine *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole and N-4-bromomethylphenylsulphonyl-L-leucinyl ethyl ether *in lieu* of N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester.

Colourless oil (20% yield after chromatography (5% methanol in DCM)):

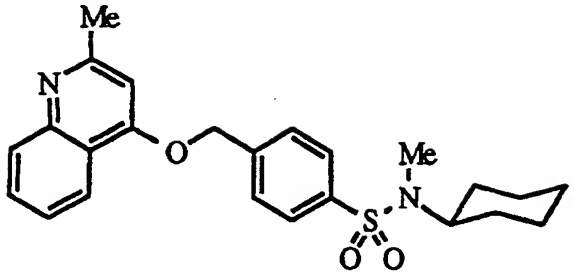
Analysis calculated for $C_{25}H_{35}N_3O_3S.1.1H_2O$
Requires C 62.89 H 7.85 N 8.80
Found C 62.69 H 7.46 N 8.55

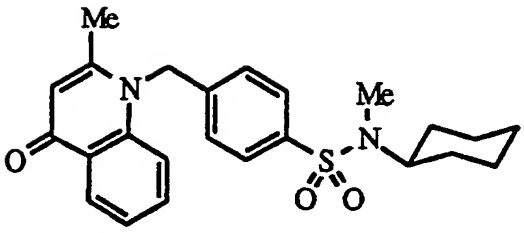
i.r. ($CDCl_3$) 3480, 3380, 2930, 2870, 1600, 1455, 1410, 1335, 1160, 1120, 1090 cm^{-1}

δ_H 8.26 (1H, s), 7.79 (2H, d, J 8.3 Hz), 7.61 (1H, d, J 7.8 Hz), 7.43-7.33 (3H, m), 7.23-7.05 (2H, m), 7.02 (1H, d, J 2.1 Hz), 5.00-4.82 (1H, m), 3.88 (2H, s), 3.43-3.10 (6H, m), 3.08-2.91 (4H, m), 1.68-1.48 (1H, m), 1.50-1.20 (2H, m), 1.07 (3H, t, J 7.0 Hz), 0.82 (3H, d, J 6.5 Hz), 0.75 (3H, d, J 6.4 Hz).

Example 61

N-Methyl-N-4-(2-methyl-4-quinolinoxy)methylphenylsulphonylcyclohexyl-amine and N-Methyl-N-4-(1H-2-methyl-4-quinone)methylphenylsulphonyl-cyclohexylamine





N-Methyl-N-4-(2-methyl-4-quinolinoxy)methylphenylsulphonylcyclohexylamine and N-Methyl-N-4-(1H-2-methyl-4-quinone)methylphenylsulphonylcyclohexylamine were prepared by the procedure of Example 4 employing 2-methyl-4-quinolinol *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole and N-methyl-N-4-bromomethylphenylsulphonylcyclohexylamine *in lieu* of N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester. The reaction gave a mixture of two regioisomers which were separated by column chromatography (5% methanol in DCM).

A) White solid foam (4% yield): m.p. 76°C

i.r. ($CDCl_3$) 2940, 2860, 2215, 1625, 1605, 1355, 1150 cm^{-1}

δ_H 8.45 (1H, dd, J 8.1, 1.7 Hz), 7.76 (2H, d, J 8.4 Hz), 7.55-7.45 (1H, m), 7.37-7.29 (1H, m), 7.20-7.14 (3H, m), 6.29 (1H, s), 5.46 (2H, s), 3.80-3.66 (1H, m), 2.72 (3H, s), 2.42 (3H, s), 1.80-1.18 (9H, m), 1.15-0.89 (1H, m).

δ_C 150.72, 141.14, 140.48, 139.98, 132.34, 127.89, 126.90, 126.74, 126.02, 123.62, 115.60, 112.31, 56.90, 49.74, 30.36, 28.61, 25.69, 25.22, 21.57.

B) White solid foam (8% yield): m.p. 158°C

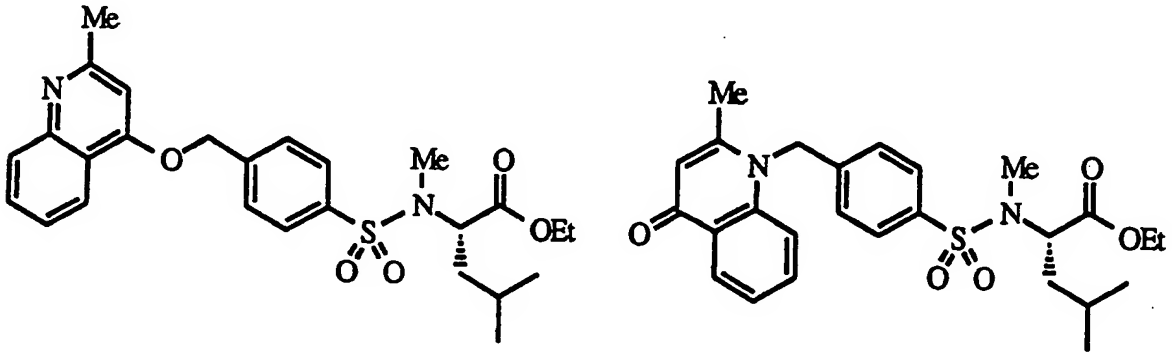
i.r. ($CDCl_3$) 2940, 2860, 2200, 1730, 1350, 1150 cm^{-1}

δ_H 8.17 (1H, dd, J 8.3, 1.3 Hz), 7.94 (1H, d, J 8.3 Hz), 7.84 (2H, d, J 8.3 Hz), 7.70-7.55 (3H, m), 7.50-7.39 (1H, m), 6.63 (1H, s), 5.28 (2H, s), 3.84-3.70 (1H, m), 2.74 (3H, s), 2.65 (3H, s), 1.80-1.18 (9H, m), 1.08-0.88 (1H, m).

δ_C 160.71, 159.89, 148.78, 140.29, 140.24, 129.84, 128.08, 127.37, 127.19, 124.93, 121.43, 119.58, 101.51, 68.89, 56.81, 30.23, 28.54, 25.82, 25.63, 25.16.

Example 62

N-Methyl-N-4-(2-methyl-4-quinolinoxy)methylphenylsulphonyl-L-leucine ethyl ester and N-Methyl-N-4-(1H-2-methyl-4-quinone)methylphenylsulphonyl-L-leucine ethyl ester



N-Methyl-N-4-(2-methyl-4-quinolinoxy)methylphenylsulphonyl-L-leucine ethyl ester and N-Methyl-N-4-(1H-2-methyl-4-quinone)methylphenylsulphonyl-L-leucine ethyl ester were prepared by the procedure of Example 30 employing 2-methyl-4-quinolinol *in lieu* of 2-mercaptobenzoxazole and N-4-bromomethylphenylsulphonyl-L-leucine ethyl ester *in lieu* of N-methyl-N-6-bromo-n-hexanoyl-L-leucine ethyl ester. The reaction gave a mixture of two regioisomers which were separated by column chromatography (5% methanol in DCM).

A) White solid foam;

B) White solid foam (13% yield):

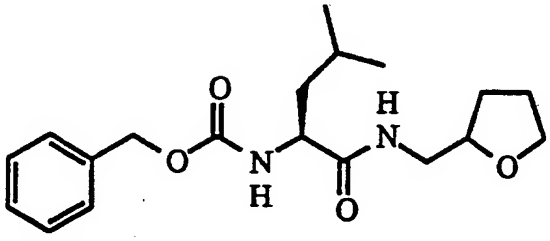
i.r. ($CDCl_3$) 3100-2800, 1730, 1595, 1340, 1150 cm^{-1}

δ_H 8.05 (1H, d, J 8.1 Hz), 7.86 (1H, d, J 8.4 Hz), 7.76 (2H, d, J 8.2 Hz), 7.57 (1H, d, J 7.4 Hz), 7.51 (2H, d, J 8.4 Hz), 7.40-7.30 (1H, m), 6.53 (1H, s), 5.16 (2H, s), 4.65-4.55 (1H, m), 3.85-3.70 (2H, m), 2.80 (3H, s), 2.58 (3H, s), 1.69-1.50 (3H, m), 0.95 (3H, t, J 7.1 Hz), 0.92 (3H, d, J 6.2 Hz), 0.87 (3H, d, J 6.2 Hz);

δ_C 170.57, 160.41, 159.67, 148.53, 140.46, 138.67, 129.56, 127.84, 127.40, 127.09, 124.65, 121.18, 119.35, 101.33, 68.62, 60.57, 59.93, 37.87, 29.57, 24.10, 22.73, 20.86, 13.61.

Example 63

N-Benzyloxycarbonyl-L-leucine tetrahydrofurfurylamide



A solution of N-benzyloxycarbonyl-L-leucine p-nitrophenyl ester (4.0 g, 10 mmol) in dry DCM (100 ml) was treated with tetrahydrofurfurylamine (4.3 ml, 42 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was washed with 1N hydrochloric acid, aqueous sodium hydrogen carbonate, water and brine, dried, filtered and evaporated. Column chromatography (1:2 hexane/ethyl acetate) gave N-benzyloxycarbonyl-L-leucine tetrahydrofurfurylamide (2.2 g, 60%) as a pale yellow oil.

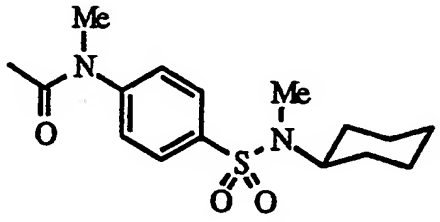
Analysis calculated for $C_{19}H_{28}N_2O_4.0.6H_2O$
Requires C 63.52 H 8.19 N 7.80
Found C 63.43 H 7.82 N 7.77

i.r. ($CDCl_3$) 1720, 1675 cm^{-1}

δ_H 7.30-7.20 (5H, m), 7.11-7.00 (1H, m), 6.05 (1H, t, J 8.0 Hz), 5.07 (1H, d, J 12.0 Hz), 5.00 (1H, d, J 12.4 Hz), 4.34-4.19 (1H, m), 3.94-3.60 (3H, m), 3.55-3.35 (1H, m), 3.25-3.04 (1H, m), 1.93-1.37 (7H, m), 0.94-0.80 (6H, br d, J 5.8 Hz).

Example 64

N-Methyl-N-4-(N'-acetyl-N'-methyl)aminophenylsulphonylcyclohexylamine



N-Methyl-N-4-(N'-acetyl-N'-methyl)aminophenylsulphonylcyclohexylamine was prepared by the method of Example 2 employing N-methyl-N-4-(N'-acetyl)-

aminophenylsulphonylcyclohexylamine *in lieu* of N-4-azidomethylphenyl-sulphonyl-L-leucine ethyl ester.

White crystalline solid (70% yield after chromatography (1:2 hexane/ethyl acetate)): m.p. 131°C

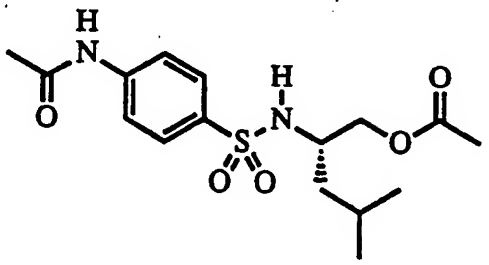
Analysis calculated for $C_{16}H_{24}N_2O_3S$
Requires C 59.23 H 7.46 N 8.63
Found C 58.83 H 7.38 N 8.53

i.r. ($CDCl_3$) 3680, 3100-2760, 1660, 1590, 1350, 1135 cm^{-1}

δ_H 7.82 (2H, d, J 8.5 Hz), 7.31 (2H, d, J 8.5 Hz), 3.83-3.69 (1H, m), 3.28 (3H, s), 2.75 (3H, s), 1.92 (3H, br s), 1.80-1.19 (9H, m), 1.10-0.90 (1H, m).

Example 65

N-4-(N'-Acetyl)aminophenylsulphonyl-L-leucinyl acetate



N-4-(N'-Acetyl)aminophenylsulphonyl-L-leucinyl acetate was prepared by the procedure of Example 8 employing N-4-(N'-acetyl)aminophenylsulphonyl-L-leucine as starting material.

Colourless foam (65% yield after chromatography (1:2 hexane/ethyl acetate)):

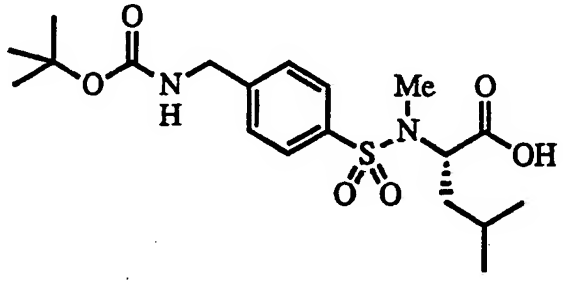
Analysis calculated for $C_{16}H_{24}N_2O_5S.0.5H_2O$
Requires C 52.59 H 6.90 N 7.67
Found C 52.66 H 6.62 N 7.56

i.r. ($CDCl_3$) 1735, 1700, 1150 cm^{-1}

δ_H 8.91 (1H, s), 7.69 (2H, d, J 8.8 Hz), 7.63 (2H, d, J 8.8 Hz), 5.76 (1H, d, J 7.7 Hz), 3.90-3.80 (2H, m), 3.54-3.40 (1H, m), 2.12 (3H, s), 1.88 (3H, s), 1.60-1.40 (1H, m), 1.36-1.13 (2H, m), 0.74 (3H, d, J 6.5 Hz), 0.65 (3H, d, J 6.4 Hz).

Example 66

N-Methyl-N-4-(N'-t-butyloxycarbonyl)aminomethylphenylsulphonyl-L-leucine



A solution of lithium hydroxide (157 mg, 3.73 mmol) in water (5 ml) was added to a solution of N-methyl-N-4-(N'-t-butyloxycarbonyl)aminomethyl-phenylsulphonyl-L-leucine ethyl ester (1.5 g, 3.39 mmol) in THF (15 ml) and the resulting mixture stirred at room temperature for 6 h. THF was removed under reduced pressure, diethyl ether (20 ml) added to the residue and the organics washed with water (2x20 ml). The combined aqueous washings were acidified (1N hydrochloric acid) and extracted with DCM (4x10 ml), dried, filtered and evaporated. Chromatography (10% methanol in DCM) gave recovered starting material (0.9 g, 60%) and N-Methyl-N-4-(N'-t-butyloxycarbonyl)amino-methylphenylsulphonyl-L-leucine (0.25 g, 18%) as a colourless oil.

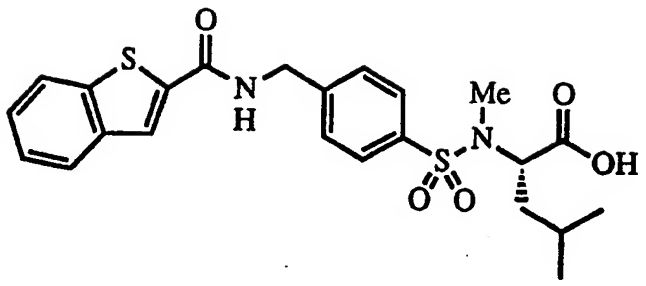
Analysis calculated for $C_{19}H_{30}N_2O_6S$
Requires C 55.05 H 7.29 N 6.76
Found C 55.14 H 7.40 N 6.71

i.r. (neat) 3400, 2960, 2860, 1740, 1520, 1360, 1170, 1020 cm^{-1}

δ_H 7.76 (2H, d, J 7.2 Hz), 7.39 (2H, d, J 7.2 Hz), 4.43 (1H, br m), 4.25 (2H, s), 2.79 (3H, s), 1.53 (3H, br m), 1.09 (9H, s), 0.87 (3H, d, J 6.3 Hz), 0.85 (3H, d, J 6.0 Hz).

Example 67

N-Methyl-N-4-(N'-2-benzo[b]thienylcarbonyl)aminomethylphenylsulphonyl-L-leucine



2M Potassium hydroxide (2.8 ml) was added to a solution of N-methyl-N-4-(N'-2-benzo[b]thienylcarbonyl)aminomethylphenylsulphonyl-L-leucine ethyl ester (2.8 g, 5.6 mmol) in ethanol (100 ml). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and water was added to the residue. The pH of the resulting solution was adjusted to pH 6 by the addition of 2M HCl. A white cloudy precipitate formed, which was extracted into ethyl acetate. A white precipitate formed and was collected by filtration and dried *in vacuo* to give N-methyl-N-4-(N'-2-benzo[b]thienylcarbonyl)aminomethylphenylsulphonyl-L-leucine (2.6 g, 99%) as a white powder

m.p. 110°C

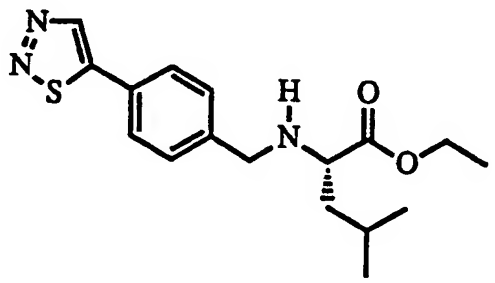
Analysis calculated for $C_{23}H_{26}N_2O_5S_2.0.5H_2O$
Requires C 57.12 H 5.63 N 5.79
Found C 57.14 H 5.46 N 5.82

i.r. (KBr) 3370, 2950, 1725, 1630, 1540, 1335, 1150 cm^{-1}

δ_H (CD_3OD) 7.96 (1H, s), 7.92-7.83 (2H, m), 7.75 (2H, d, J 8.4 Hz), 7.51 (2H, d, J 8.3 Hz), 7.45-7.34 (2H, m), 4.62 (2H, s), 4.63-4.52 (1H, m), 3.29-3.26 (1H, m), 2.79 (3H, s), 2.63-2.49 (3H, m), 0.90 (6H, d, J 5.4 Hz).

Example 68

N-4-(1,2,3-Thiadiazol-5-yl)phenylmethyl-L-leucine ethyl ester



Triethylamine (11 ml) was added to a stirred mixture of L-leucine ethyl ester hydrochloride (11.0 g, 59 mmol) in dry THF (200 ml) at room temperature. After 10 min. 5-(4-bromomethylphenyl)-1,2,3-thiadiazole (5.0 g, 20 mmol) was added and the mixture stirred at room temperature for 3 days. Saturated aqueous ammonium chloride was added and the mixture extracted with ethyl acetate. The combined organic extracts were washed with aqueous citric acid and brine, dried, filtered and concentrated. Chromatography (1:4 ethyl acetate/hexane) gave N-4-(1,2,3-thiadiazol-5-yl)phenylmethyl-L-leucine ethyl ester (3.41 g, 51%) as a colourless oil.

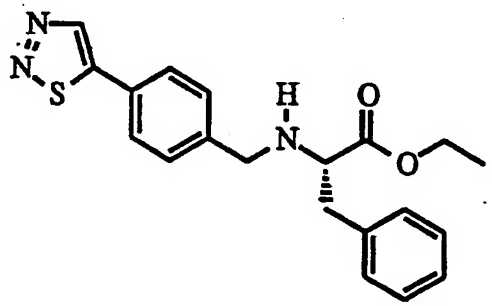
Analysis calculated for $C_{17}H_{23}N_3O_2S$
Requires C 61.23 H 6.96 N 12.61
Found C 61.02 H 6.85 N 12.76

i.r. ($CDCl_3$) 1725 cm^{-1}

δ_H 8.62 (1H, s), 7.96(2H, d, J 8.2 Hz), 7.44 (2H, d, J 8.2 Hz), 4.17 (2H, q, J 7.0 Hz), 3.86 (1H, d, J 13.3 Hz), 3.64 (1H, d, J 13.3 Hz), 3.28 (1H, m), 1.93-1.70 (2H, m), 1.55-1.40 (2H, m), 1.27 (3H, t, J 7.0 Hz), 0.90 (3H, d, J 6.7 Hz), 0.83 (3H, d, J 6.6 Hz).

Example 69

N-4-(1,2,3-Thiadiazol-5-yl)phenylmethyl-L-phenylalanine ethyl ester



N-4-(1,2,3-Thiadiazol-5-yl)phenylmethyl-L-phenylalanine ethyl ester was prepared by the method of Example 68 employing L-phenylalanine ethyl ester hydrochloride *in lieu* of L-leucine ethyl ester hydrochloride.

Yellow oil (53% yield after chromatography (2:1 hexane/ethyl acetate)):

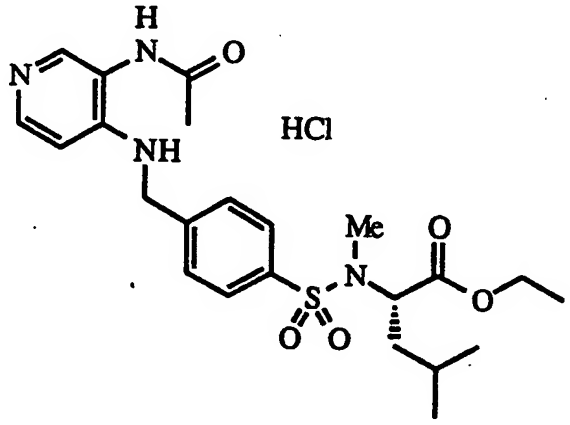
Analysis calculated for $C_{20}H_{21}N_3O_2S.0.2H_2O$
Requires C 64.74 H 5.81 N 11.32
Found C 64.85 H 5.82 N 11.37

i.r. ($CDCl_3$) 2980, 2220, 1725, 1445, 1180 cm^{-1}

δ_H 8.61 (1H, s), 7.95 (2H, d, J 8.2 Hz), 7.36 (2H, d, J 8.2 Hz), 7.29-7.18 (5H, m), 4.14 (2H, q, J 7.1 Hz), 3.90 (1H, d, J 13.6 Hz), 3.71 (1H, d, J 13.6 Hz), 3.55 (1H, t, J 7.0 Hz), 2.99 (2H, d, J 6.9 Hz), 1.19 (3H, t, J 7.1 Hz).

Example 70

N-Methyl-N-4-(N'-3-N''-acetylaminopyrid-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester hydrochloride



(a) N-Methyl-N-4-(N'-3-aminopyrid-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester

A solution of N-methyl-N-4-(N'-3-nitropyrid-4-yl)aminomethylphenyl-sulphonyl-L-leucine ethyl ester (10.9 g, 0.023 mol) in ethanol (40 ml) was hydrogenated at 100 p.s.i. overnight in the presence of 10% palladium on charcoal (1.0 g). The catalyst was removed by filtration through GF/F filter paper, and the filtrate evaporated under reduced pressure to give N-methyl-N-4-(N'-3-aminopyrid-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester (8.90 g, 87%) as a brown foam.

δ_H 7.86 (1H, s) 7.83 (1H, d, J 5.5 Hz), 7.73 (2H, d, J 8.3 Hz), 7.41 (2H, d, J 8.3 Hz), 6.29 (1H, d, J 5.4 Hz), 5.04 (1H, m), 4.67-4.61 (1H, m), 4.44 (2H, d, J 5.6 Hz), 3.90-3.81 (2H, m), 3.73-3.46 (2H, br s), 2.84 (3H, s), 1.62-1.57 (3H, m), 1.04 (3H, t, J 7.1 Hz), 0.96 (3H, d, J 6.0 Hz), 0.95 (3H, d, J 6.1 Hz).

(b) N-Methyl-N-4-(N'-3-N''-acetylaminopyrid-4-yl)aminomethylphenyl-sulphonyl-L-leucine ethyl ester hydrochloride

Acetyl chloride (70 µl, 1.0 mmol) was added to a stirred solution of N-methyl-N-4-(N'-3-aminopyrid-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester (405 mg, 0.9 mmol) in dry THF at room temperature under argon. After 1 h stirring was stopped and the reaction mixture was placed in a freezer. A white solid precipitate which had formed was collected by filtration and dried *in vacuo* to give N-methyl-N-4-(N'-3-N"-acetylaminopyrid-4-yl)aminomethyl-phenylsulphonyl-L-leucine ethyl ester hydrochloride (267 mg, 56%) as a white crystalline solid.

m.p. 167-170°C

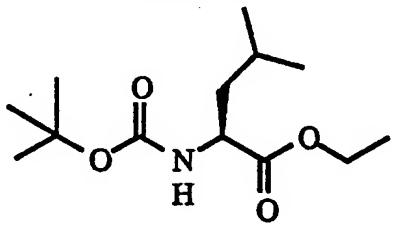
i.r. ($CDCl_3$) 3380-3090, 2960, 1735, 1700, 1340, 1150 cm^{-1}

δ_H 8.97 (1H, br s), 8.81 (1H, d, J 5.7 Hz), 7.77-7.73 (3H, m), 7.49 (2H, d, J 8.0 Hz), 6.53 (1H, d, J 6.7 Hz), 4.70-4.62 (3H, m), 3.91 (2H, q, J 7.1 Hz), 3.79-3.72 (1H, br m), 2.82 (3H, s), 2.38 (3H, s), 1.66-1.55 (3H, br m), 1.09 (3H, t, J 7.1 Hz), 1.00-0.92 (6H, br d);

δ_C 170.97, 170.85, 151.03, 140.53, 138.89, 135.48, 128.06, 127.46, 105.68, 61.04, 57.28, 46.23, 38.07, 29.82, 24.44, 24.10, 23.07, 21.12.

Example 71

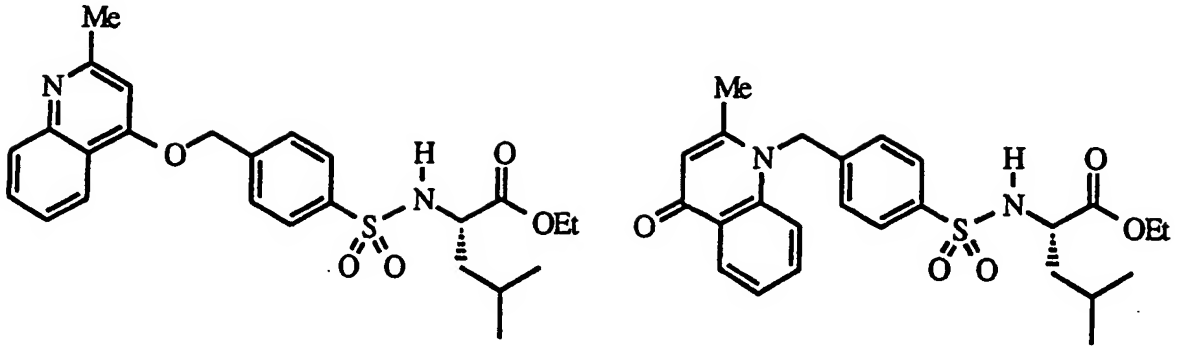
N-t-Butyloxycarbonyl-L-leucine ethyl ester



N-t-Butyloxycarbonyl-L-leucine ethyl ester was obtained commercially.

Example 72

N-4-(2-Methyl-4-quinolinoxy)methylphenylsulphonyl-L-leucine ethyl ester and N-4-(1H-2-methyl-4-quinone)methylphenylsulphonyl-L-leucine ethyl ester



N-4-(2-Methyl-4-quinolinoxy)methylphenylsulphonyl-L-leucine ethyl ester and N-4-(1H-2-methyl-4-quinone)methylphenylsulphonyl-L-leucine ethyl ester were prepared by the procedure of Example 4 employing 2-methyl-4-quinolinol *in lieu* of 3-mercapto-4-methyl-5-(2-thienyl)-1,2,4-triazole. The reaction gave a mixture of two regioisomers which were separated by column chromatography (5% methanol in DCM).

A) White solid foam;

B) White solid foam (5% yield):

i.r. ($CDCl_3$) 3345, 2965, 1735, 1625, 1605, 1490, 1425, 1350, 1315 cm^{-1}

δ_H 8.40 (1H, d, J 7.5 Hz), 7.77 (1H, d, J 8.2 Hz), 7.45 (1H, br t, J 7.2 Hz), 7.28 (1H, br t, J 7.6 Hz), 7.20-7.10 (3H, m), 6.25 (1H, s), 5.70-5.60 (1H, m), 5.43 (2H, s), 3.94-3.70 (3H, m), 2.36 (3H, s), 1.80-1.60 (1H, m), 1.56-1.40 (2H, m), 0.99 (3H, t, J 7.2 Hz), 0.84 (3H, d, J 6.6 Hz), 0.82 (3H, d, J 6.5 Hz);

δ_C 177.55, 171.88, 150.67, 141.11, 140.67, 140.11, 132.17, 128.13, 126.83, 125.93, 123.43, 115.53, 112.21, 61.18, 54.50, 49.61, 42.16, 24.26, 22.55, 21.34, 13.78.

Example 73

Inhibition of [^{3}H]-PAF Receptor Binding

The inhibition of [^{3}H]-PAF binding to human platelet plasma membrane by compounds of general formula I was determined by isotopic labelling and filtration techniques. Platelet concentrates were obtained from a hospital blood bank. These platelet concentrates (500-2500 ml.) were centrifuged at 800 rpm for 10 minutes in a SORVALL RC3B centrifuge to remove the red blood cells present. (The word SORVALL is a trade mark.) The supernatant was subsequently centrifuged at 3,000 rpm in a SORVALL RC3B centrifuge to

pellet the platelets present. The platelet rich pellets were resuspended in a minimum volume of buffer (150 mM NaCl, 10 mM Tris, 2 mM EDTA, pH 7.5) and layered onto Ficoll-Paque gradients, 9 ml platelet concentrate to 2 ml Ficoll, and centrifuged at 1,900 rpm for 15 minutes in a SORVALL RT6000 centrifuge. This step removes the residual red blood cells and other nonspecific material such as lymphocytes from the preparation. The platelets which form a band between the plasma and the Ficoll were removed, resuspended in the above buffer and centrifuged at 3,000 rpm for 10 minutes in a SORVALL RT6000 centrifuge. The pelleted platelets were resuspended in buffer (10 mM Tris, 5mM $MgCl_2$, 2 mM EDTA, pH 7.0), snap freezed in liquid N_2 and allowed to thaw slowly at room temperature in order to lyse the platelets. The latter step was repeated at least 3 times to ensure proper lysis. The lysed platelets were centrifuged at 3,000 rpm for 10 minutes in a SORVALL RT6000 centrifuge and resuspended in buffer. The latter step was repeated twice in order to remove any cytoplasmic proteins which may hydrolyse the platelet activating factor (PAF) receptor. The prepared platelet membranes may be stored at -70°C. After thawing the prepared membranes were centrifuged in a SORVALL RT6000 at 3,000 rpm for 10 minutes and resuspended in assay buffer.

The assay was conducted by preparing a series of Tris-buffered solutions of the selected antagonist of predetermined concentrations. Each of these solutions contained [^{3}H]-PAF (0.5 nM; 1-*O*-[^{3}H]octadecyl-2-acetyl-*sn*-glycero-3-phosphoryl choline with a specific activity of 132 Ci/mmol), unlabelled PAF (1000 nM), a known amount of the test antagonist, and a sufficient amount of Tris-buffer solution (10mM Tris, 5mM $MgCl_2$, pH 7.0, 0.25% BSA) to make the final volume 1ml. Incubation was initiated by the addition of 100 5g of the isolated membrane fraction to each of the above solutions at 0°C. Two control samples, one (C1) which contained all the ingredients described above except the antagonist and the other (C2) contains C1 plus a 1000-fold excess of unlabelled PAF, were also prepared and incubated simultaneously with the test samples. After 1 hour incubation, each solution was filtered rapidly under *vacuo* through a WHATMAN GF/C glass fibre filter in order to separate unbound PAF from bound PAF. (The word WHATMAN is a trade mark.) The residue in each case was rapidly washed 4 times with 5 ml cold (4°C) Tris-buffer solution. Each washed residue was dried under vacuum on a sampling manifold and placed into vials containing 20 ml of OPTIPHASE MP scintillation fluid and the radioactivity counted in a liquid scintillation counter. (The word OPTIPHASE is a trade mark.) Defining the counts for total binding with antagonist from a test sample as "TBA"; the counts for total binding from the control sample C1 as

"TB"; and the counts for nonspecific binding from the control sample C2 as "NSB", the percent inhibition of each test antagonist can be determined by the following equation:

%Inhibition = [(TB-TBA)/SB]x100

where the specific binding SB = TB-NSB

Table 1 lists results from this assay for inhibition of [^{3}H]-PAF receptor binding for illustrative examples of the compounds of this invention.

Table 1: Results for inhibition of [^{3}H]-PAF receptor binding

Example	Inhibition of [^{3}H]-PAF binding IC_{50} nM
3	100
5	10
8	10
18	10
21	5
24	25
25	60
27	10
28	90
32	1
38	3
49	6
50	7
55	5
59	2
68	5
70	50
71	150

Example 74

Inhibition of PAF-Induced Hypotension in the Rat

The activity of the compounds of general formula I is also demonstrated *in vivo* by their ability to reverse the hypotension caused by an infusion of PAF in rats. Male Sprague-Dawley rats (300-350 g) were anaesthetised with a mixture of sodium pentobarbitone, 22.5 mg/kg and thiopental 62.5 mg/kg. Through a midline incision in the neck, the trachea was cannulated and the animals breathed spontaneously. A carotid artery was cannulated for the measurement of blood pressure and this signal was used to trigger a rate meter to measure heart rate. Both jugular veins were cannulated: one for the infusion of PAF and the other for the bolus administration of test compounds.

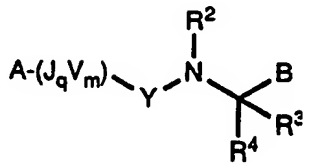
PAF, 100 ng/kg/min was infused *i.v.* until a sustained fall in mean blood pressure of 50 mmHg was achieved. Test compounds were administered *i.v.* as a bolus and resulted in a dose dependent reversal of the PAF induced hypotension. The peak of this reversal was measured and the dose to cause a 50% reversal of the hypotensive PAF response (ED_{50}) calculated by straight line interpolation and the results are presented in Table 2.

Table 2: Results for inhibition of PAF-induced hypotension in the rat

Example	ED_{50} (μg/kg *i.v.*)
15	180
41	41% inhibition @ 1 mg/kg
62B	7.3

CLAIMS

1. A compound of general formula I:



I

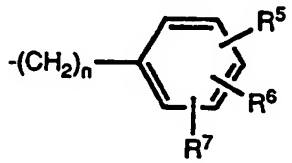
wherein:

A represents:

a) a group -Q-X wherein Q represents an -O-, -S- or -NR- group (wherein R is as defined below) or a bond; and

X represents a 5- or 6-membered aromatic or heterocyclic ring, which may optionally be fused to a benzene ring or to a further 5- or 6-membered aromatic or heterocyclic ring and wherein any of the rings may be optionally substituted with one or more substituents; and

optional substituents of the rings of the group X are -CN, -NO_2, halogen, -C_1-C_4 perfluoroalkyl, hydroxyl, carbonyl, thiocarbonyl, carboxyl, -$CONH_2$, a group -D wherein D is as defined below, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO_2R^{11}, -NHR^{11}, -$NR^{11}R^{11}$, CO_2R^{11} or -$CONHR^{11}$ wherein R^{11} is -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_8 cycloalkyl or -C_4-C_8 cycloalkenyl each of which is optionally substituted with one or more substituents selected from halogen, hydroxyl, amino, carboxyl, -C_1-C_4 perfluoroalkyl, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, tetrazol-5-yl, a heteroaryl or heteroarylmethyl group or a group -D



wherein n is an integer from 0 to 3, and each of R^5, R^6 and R^7 is independently hydrogen, -C_1-C_6 alkyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -$N(C_1$-C_6 alkyl$)_2$, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -OCH_2Ph, halogen, -CN, -CF_3, -CO_2H, -CO_2C_1-C_6 alkyl, -$CONH_2$, -$CONHC_1$-C_6 alkyl, -$CON(C_1$-C_6 alkyl$)_2$, -CHO, -CH_2OH, -NH_2, -$NHCOC_1$-C_6 alkyl, -SOC_1-C_6 alkyl, or -SO_2C_1-C_6 alkyl; or

b) a group -CN, -NO_2, -N_3 -NRR^1, -OR, -C(=O)NHCHRR^1, -C(=O)NRR^1, -NRC(=O)R^1, -NRC(=O)OR^1, -S(=O)$_2$NHCHRR^1, -S(=O)$_2$NRR^1, -COR, -CO_2R, -SO_2R, -SOR, -COX, -SO_2X, wherein X is as defined above, or a halogen atom;

each of R and R^1 independently represents a hydrogen atom, -C_1-C_{18} alkyl, -C_2-C_{18} alkenyl, -C(=O)C_1-C_8 alkyl, -C(=O)OC_1-C_8 alkyl, -C(=O)OC_2-C_8 alkenyl, a group -D as defined above, or -(C_1-C_8 alkyl)X wherein X is as defined above;

J represents a divalent alkanediyl, alkenediyl or alkynediyl group from 1 to 8 carbon atoms which may be a straight or branched-chain, wherein the said group is either unsubstituted or substituted by one or more substituents selected from hydroxy, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, halogen, -CF_3, and -CN;

q is 0 or 1;

V represents a phenylene, furandiyl, tetrahydrofurandiyl, thiophenediyl, tetrahydothiophenediyl, thiazolediyl or tetrahydothiazolediyl group, wherein the said group is either unsubstituted or substituted by one or more substituents selected from hydroxy, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, halogen, -CF_3, and -CN;

m is 0 or 1;

Y represents a bond, a -CH_2-, -C(=O)-, -C(=S)-, -S(=O)$_2$- or -P(=O)(OC_1-C_6 alkyl)- group provided that when Y is -S(=O)$_2$- the group Q is not a bond;

R^2 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -CO_2C_1-C_6 alkyl, -CO_2(C_1-C_6 alkyl)phenyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)phenyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or a group -D wherein D is as defined above;

or R^2 together with R^3 and the atoms to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

each of R^3 and R^4 may independenly represent hydrogen, halogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)N(C_1-C_6 alkyl)$_2$, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8

cycloalkyl, -(C_1-C_6 alkyl)C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)OC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)OC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)SC_3-C_8 cycloalkyl or -(C_1-C_6 alkyl)SC_4-C_8 cycloalkenyl (any of which may optionally be substituted with one or more substituents selected from halogen, hydroxyl, nitro, nitrile or carboxyl), a side chain of a naturally occurring amino acid, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

or R^3 and R^4 together with the carbon atom to which they are attached form a C_3-C_8 cycloalkyl ring;

B represents:

a) a ZR^8 group wherein Z is a bond, -C(=O)-, -C(=O)O-, -CH_2O-, -CH_2OC(=O)-, -C(=S)-, -C(=S)O-, -CH_2S-, -CH_2OC(=O)NH-, -C(=O)NHSO_2- or -SO_2NHC(=O)- and;

R^8 is hydrogen, -C_1-C_{18} alkyl, -C_2-C_{18} alkenyl, -C_2-C_{18} alkynyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)OC_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or pyridyl, (any of which may optionally be substituted with one or more substituents selected from halogen, hydroxyl, nitro, nitrile or carboxyl), -C_1-C_4 perfluoroalkyl, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

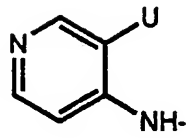
b) a -$CH_2NR^9R^{10}$ group or a -$CONR^9R^{10}$ group wherein each of R^9 and R^{10} is independently hydrogen, -C_1-C_{18} alkyl, -C_2-C_{18} alkenyl, -C_2-C_{18} alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or pyridyl (any of which may optionally be substituted with one or more substituents selected from halogen, hydroxyl, nitro, nitrile or carboxyl) or a group -D as defined above;

or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

c) a group E where E is a 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from nitrogen, oxygen and sulphur, which may optionally be fused to a benzene ring, and the ring may be optionally substituted with one or more substituents selected from -C_1-C_6 alkyl, -OC_1-C_6 alkoxy, halogen, -CF_3 and -CN; or

d) a group -CH_2E, -C(=O)NHE or -C(=O)$NHCH_2E$, wherein E is as defined above;

provided that when A is a group:



wherein U is -NO_2 or -NH_2 and J is a group -CHR- wherein R is as defined above; or

when A is OMe, -NHCOMe, -NO_2 or -CN, q is 0, Y is -SO_2- or -CO- and Z is other than a bond or a -C(=O)O- group; or

when A is -N_3, J is -CH_2- and Y is -SO_2-;

then V is not a 1,4-phenylene group; and

provided that when q is 0, m is 0 and Z is other than a bond or a -C(=O)O- group, then the grouping AY- is other than t-butyloxycarbonyl or benzyloxycarbonyl;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

2. A compound as claimed in claim 1 wherein A represents a group -Q-X in which

Q is as defined in claim 1;

X represents a pyridyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indolyl, quinolinyl, triazolyl, phenyl, furanyl, thiazolyl, thiadiazolyl or a oxadiazolyl group, all these groups being optionally substituted as defined for general formula I; or

A represents a -CN, -NO_2, -N_3, -NRR^1, -OR, -C(=O)$NHCHRR^1$, -S(=O)2$NHCHRR^1$, -COR, -CO_2R, -$NRC(=O)R^1$, -$NRC(=O)OR^1$, -COX or -SO_2X group;

wherein R represents a hydrogen atom, a -C_1-C_{18} alkyl group, a phenyl group, a -C(=O)C_1-C_8 alkyl group, a group -D, or a -(C_1-C_8 alkyl)X group; and

wherein R^1 represents a hydrogen atom, a -C_1-C_8 alkyl group or a -C(=O)OC_1-C_8 alkyl group;

3. A compound as claimed in claim 1 or claim 2 wherein J represents a -C_1-C_8 alkanediyl group.

4. A compound as claimed in any one of claims 1 to 3 wherein V represents a phenylene, substituted phenylene group or a thiophenediyl group.

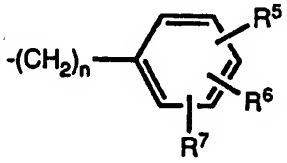
5. A compound as claimed in any one of claims 1 to 4 wherein Y represents a bond, a -CH_2-, -C(=O)- or -S(=O)$_2$- group.

6. A compound as claimed in any one of claims 1 to 5 wherein R^2 represents a hydrogen atom, a -C_1-C_6 alkyl group, a group -D or, together with R^3 and the atoms to which they are attached, forms a 5 to 8 membered nitrogen-containing heterocyclic ring.

7. A compound as claimed in any one of claims 1 to 6 wherein R^3 represents a hydrogen atom, a -C_1-C_6 alkyl group, a -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl group, the side chain of a naturally occurring amino acid, a group -D or R^3, together with R^2 and the atoms to which they are attached, forms a 5 to 8 membered nitrogen-containing heterocyclic ring or together with R^4 and the carbon atom to which they are attached forms a C_3-C_8 cycloalkyl ring.

8. A compound as claimed in any one of claims 1 to 7 wherein R^4 represents a hydrogen atom, a group -D or, together with R^3 and the carbon atom to which they are attached, forms a C_3-C_8 cycloalkyl ring.

9. A compound as claimed in any one of claims 1 to 8, in which a group D is present in any of the specified substituents, wherein D represents a



group wherein;

n represents an integer of 0, 1 or 3 and R^5, R^6 and R^7 are as defined in claim 1.

10. A compound as claimed in claim 9 wherein each of R^5, R^6 and R^7 represents a hydrogen atom.

11. A compound as claimed in any one of claims 1 to 10 wherein B represents a ZR^8 group, wherein Z and R^8 are as defined in claim 1, a group E, a $-CH_2E$ group or a $-(C=O)NHCH_2E$ group, wherein E is as defined in claim 1.

12. A compound as claimed in claim 11 wherein Z represents a bond, a $-C(=O)O-$ group, a $-CH_2O-$ group or a $-CH_2OC(=O)-$ group.

13. A compound as claimed in claim 11 or claim 12 wherein R^8 represents hydrogen atom, a $-C_1-C_{18}$ alkyl, $-C_2-C_{18}$ alkenyl or a $-(C_1-C_6$ alkyl$)OC_1-C_6$ alkyl group.

14. A compound as claimed in claim 11 wherein E represents a tetrahydrofuranyl, an indolyl or a tetrazolyl group.

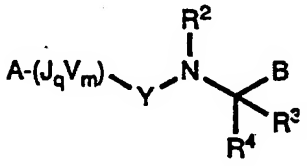
15. N-4-(4-Methyl-5-(2-thienyl)-1,2,4-triazol-3-yl)thiomethylphenyl-sulphonyl-L-leucine ethyl ester,
N-4-(N'-3,4-Dimethoxyphenyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucine ethyl ester,
N-Methyl-N-4-(N'-3,4-dimethoxyphenyl)aminomethylphenylsulphonyl-3-aminopropionic acid ethyl ester,
N-Methyl-N-4-(N'-(3,4-dimethoxyphenyl)-N'-acetyl)aminomethylphenyl-sulphonyl-3-aminopropionic acid ethyl ester,
N-4-(Benzthiazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl methyl ether,
N-4-(Benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl ethyl ether,
N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl ethyl ether,
N-Methyl-N-4-(4-methyl-5-methylthio-1,2,4-triazol-3-yl)thiomethyl-phenylsulphonyl-L-leucinyl ethyl ether,
N-4-(5-(2-Pyridyl)-1,3,4-oxadiazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl ethyl ether,
N-Methyl-N-4-(N'-benzthiazol-2-yl)aminomethylphenylsulphonyl-L-leucinyl ethyl ether,
N-4-(Benzoxazol-2-yl)thiomethylphenylsulphonyl-L-leucinyl methoxyethyl ether,

N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylcarbonyl-L-leucinyl ethyl ether,
N-Benzyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-2-phenylethylamine,
N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-1,2-diphenylethylamine,
N-Methyl-N-4-(5-chlorobenzoxazol-2-yl)thiomethylphenylsulphonyl-1,2-diphenylethylamine,
N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylcarbonyl-cyclohexylamine,
N-Methyl-N-4-(benzoxazol-2-yl)thiomethylphenylsulphonyl-cyclohexylamine,
N-3-(Benzoxazol-2-yl)thiopropylsulphonylmorpholine,
N-4-(4,5-Dihydrothiazol-2-yl)thiomethylphenylsulphonyl-L-leucine ethyl ester,
N-4-(N'-Benzimidazol-2-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
N-4-(N'-3-Phenylpropyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
N-4-(N'-Heptyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
N-Methyl-N-6-(benzoxazol-2-yl)thiohexanoyl-L-leucine ethyl ester,
N-Methyl-N-4-(N'-hexanoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
N-Methyl-N-4-(N'-hexadecanoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
N-Methyl-N-4-(N'-4-methoxybenzoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
N-Methyl-N-4-(N'-3,5-dimethoxybenzoyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
N-Methyl-N-4-(N'-furan-2-ylcarbonyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
N-Methyl-N-4-(N'-acetyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
N-Methyl-N-4-(N'-t-butyloxycarbonyl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
N-4-(N'-Acetyl)amino-3-fluorophenylsulphonyl-L-leucine ethyl ester,
N-4-(N'-Acetyl)aminophenylsulphonyl-L-leucinyl ethyl ether,
N-4-(N'-Acetyl)aminophenylsulphonyl-L-leucinol,
N-4-n-Butoxyphenylcarbonyl-L-leucine ethyl ester,
N-3,4,5-Triethoxyphenylcarbonyl-L-leucine ethyl ester,
N-4-Phenylbutanoyl-L-leucine ethyl ester,
1,3-Di(N-sulphonyl-L-leucine ethyl ester)benzene,
N-3-(O-Ethyl-L-leucinecarboxy)phenylsulphonyl-L-leucine ethyl ester,
N-4-(Hydroxycarbonyl)phenylsulphonyl-L-leucine ethyl ester,
N-4-(N'-Acetyl)aminophenylsulphonyltetrahydrofurfurylamine,
N-4-(N'-Acetyl)aminophenylsulphonyltryptamine,
5-(Phenylsulphonyl)thien-2-ylsulphonyl-L-leucine ethyl ester,

N-Methyl-N-4-(N'-4-(N''-acetyl)aminophenylsulphonyl)aminomethyl-phenylsulphonyl-L-leucine ethyl ester,
N-Methyl-N-4-(N'-2-benzo[b]thienylcarbonyl)aminomethylphenyl-sulphonyl-L-leucine ethyl ester,
N-4-(N'-2-Indolol-3-ylethyl)aminomethylphenylsulphonyl-L-leucinyl ethyl ether,
N-Methyl-N-4-(2-methyl-4-quinolinoxy)methylphenylsulphonylcyclo-hexylamine,
N-Methyl-N-4-(2-methyl-4-quinolinoxy)methylphenylsulphonyl-L-leucine ethyl ester,
N-Benzyloxycarbonyl-L-leucine tetrahydrofurfurylamide,
N-Methyl-N-4-(N'-acetyl-N'-methyl)aminophenylsulphonylcyclohexylamine,
N-4-(N'-Acetyl)aminophenylsulphonyl-L-leucinyl acetate,
N-Methyl-N-4-(N'-t-butyloxycarbonyl)aminomethylphenylsulphonyl-L-leucine,
N-Methyl-N-4-(N'-2-benzo[b]thienylcarbonyl)aminomethylphenyl-sulphonyl-L-leucine,
N-4-(1,2,3-Thiadiazol-5-yl)phenylmethyl-L-leucine ethyl ester,
N-4-(1,2,3-Thiadiazol-5-yl)phenylmethyl-L-phenylalanine ethyl ester,
N-Methyl-N-4-(N'-3-N''-acetylaminopyrid-4-yl)aminomethylphenylsulphonyl-L-leucine ethyl ester,
N-4-(2-Methyl-4-quinolinoxy)methylphenylsulphonyl-L-leucine ethyl ester,

or a salt of such a compound.

16. A compound of general formula I



I

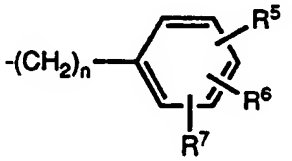
wherein:

A represents:

a) a group -Q-X wherein Q represents an -O-, -S- or -NR- group (wherein R is as defined below) or a bond; and

X represents a 5- or 6-membered aromatic or heterocyclic ring, which may optionally be fused to a benzene ring or to a further 5- or 6-membered aromatic or heterocyclic ring and wherein any of the rings may be optionally substituted with one or more substituents; and

optional substituents of the rings of the group X are -CN, -NO_2, halogen, -C_1-C_4 perfluoroalkyl, hydroxyl, carbonyl, thiocarbonyl, carboxyl, -$CONH_2$, a group -D wherein D is as defined below, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO_2R^{11}, -NHR^{11}, -$NR^{11}R^{11}$, CO_2R^{11} or -$CONHR^{11}$ wherein R^{11} is -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_8 cycloalkyl or -C_4-C_8 cycloalkenyl each of which is optionally substituted with one or more substituents selected from halogen, hydroxyl, amino, carboxyl, -C_1-C_4 perfluoroalkyl, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, tetrazol-5-yl, a heteroaryl or heteroarylmethyl group or a group -D



wherein n is an integer from 0 to 3, and each of R^5, R^6 and R^7 is independently hydrogen, -C_1-C_6 alkyl, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -$N(C_1$-C_6 alkyl$)_2$, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -OCH_2Ph, halogen, -CN, -CF_3, -CO_2H, -CO_2C_1-C_6 alkyl, -$CONH_2$, -$CONHC_1$-C_6 alkyl, -$CON(C_1$-C_6 alkyl$)_2$, -CHO, -CH_2OH, -NH_2, -$NHCOC_1$-C_6 alkyl, -SOC_1-C_6 alkyl, or -SO_2C_1-C_6 alkyl; or

b) a group -CN, -NO_2, -N_3 -NRR^1, -OR, -$C(=O)NHCHRR^1$, -$C(=O)NRR^1$, -$NRC(=O)R^1$, -$NRC(=O)OR^1$, -$S(=O)_2NHCHRR^1$, -$S(=O)_2NRR^1$, -COR, -CO_2R, -SO_2R, -SOR, -COX, -SO_2X, wherein X is as defined above, or a halogen atom;

each of R and R^1 independently represents a hydrogen atom, -C_1-C_{18} alkyl, -C_2-C_{18} alkenyl, -$C(=O)C_1$-C_8 alkyl, -$C(=O)OC_1$-C_8 alkyl, -$C(=O)OC_2$-C_8 alkenyl, a group -D as defined above, or -(C_1-C_8 alkyl)X wherein X is as defined above;

J represents a divalent alkanediyl, alkenediyl or alkynediyl group from 1 to 8 carbon atoms which may be a straight or branched-chain, wherein the said group is either unsubstituted or substituted by one or more substituents selected from hydroxy, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, halogen, -CF_3, and -CN;

q is 0 or 1;

V represents a phenylene, furandiyl, tetrahydrofurandiyl, thiophenediyl, tetrahydothiophenediyl, thiazolediyl or tetrahydothiazolediyl group, wherein the said group is either unsubstituted or substituted by one or more substituents selected from hydroxy, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, halogen, -CF_3, and -CN;

m is 0 or 1;

Y represents a bond, a -CH_2-, -C(=O)-, -C(=S)-, -$S(=O)_2$- or -P(=O)(OC_1-C_6 alkyl)- group provided that when Y is -$S(=O)_2$- the group Q is not a bond;

R^2 represents hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -COC_1-C_6 alkyl, -CO_2C_1-C_6 alkyl, -CO_2(C_1-C_6 alkyl)phenyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)phenyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or a group -D wherein D is as defined above;

or R^2 together with R^3 and the atoms to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

each of R^3 and R^4 may independenly represent hydrogen, halogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)N(C_1-C_6 alkyl)2, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)OC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)OC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)SC_3-C_8 cycloalkyl or -(C_1-C_6 alkyl)SC_4-C_8 cycloalkenyl (any of which may optionally be substituted with one or more substituents selected from halogen, hydroxyl, nitro, nitrile or carboxyl), a side chain of a naturally occurring amino acid, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

or R^3 and R^4 together with the carbon atom to which they are attached form a C_3-C_8 cycloalkyl ring;

B represents:

a) a ZR^8 group wherein Z is a bond, -C(=O)-, -C(=O)O-, -CH_2O-, -CH_2OC(=O)-, -C(=S)-, -C(=S)O-, -CH_2S-, -CH_2OC(=O)NH-, -C(=O)$NHSO_2$- or -SO_2NHC(=O)- and;

R^8 is hydrogen, -C_1-C_{18} alkyl, -C_2-C_{18} alkenyl, -C_2-C_{18} alkynyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)O(C_1-C_6 alkyl)OC_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or pyridyl, (any of which may optionally be substituted with one or more substituents selected from halogen, hydroxyl, nitro, nitrile or carboxyl), -C_1-C_4 perfluoroalkyl, a group -D as defined above or a -(C_1-C_6 alkyl)OD group wherein D is as defined above;

b) a -$CH_2NR^9R^{10}$ group or a -$CONR^9R^{10}$ group wherein each of R^9 and R^{10} is independently hydrogen, -C_1-C_{18} alkyl, -C_2-C_{18} alkenyl, -C_2-C_{18} alkynyl, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl or pyridyl (any of which may optionally be substituted with one or more substituents selected from halogen, hydroxyl, nitro, nitrile or carboxyl) or a group -D as defined above;

or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

c) a group E where E is a 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from nitrogen, oxygen and sulphur, which may optionally be fused to a benzene ring, and the ring may be optionally substituted with one or more substituents selected from -C_1-C_6 alkyl, -OC_1-C_6 alkoxy, halogen, -CF_3 and -CN; or

d) a group -CH_2E, -C(=O)NHE or -C(=O)NHCH_2E, wherein E is as defined above;

or a pharmaceutically or veterinarily acceptable salt thereof for use in medicine.

17. A compound as claimed in any one of claims 2 to 15 for use in medicine.

18. A compound as claimed in claim 16 or claim 17 for use in the treatment or prophylaxis of diseases or conditions mediated by PAF.

19. A compound as claimed of general formula I as claimed in claim 1 wherein the group A possesses at least one -C_1-C_6 alkyl substituent, -(J_qV_m)- is a 1,4- substituted -$CH_2C_6H_4$- group and B represents a -C(=O)OH group, a -C(=O)NHSO_2C_1-C_6 alkyl group, a -C(=O)NHSO_2C_1-C_4 perfluoroalkyl group, a tetrazolyl group or a -C(=O)NHtetrazolyl group for use in the treatment or prophylaxis of diseases or conditions mediated by angiotensin II.

20. The use of a compound of general formula I wherein A, J, q, V, m, Y, R^2, R^3, R^4 and B are as defined in claim 16, a pharmaceutically or veterinarily acceptable salt thereof or a compound as claimed in any one of claims 2 to 15 in the preparation of an agent for the treatment or prophylaxis of diseases or conditions mediated by PAF.

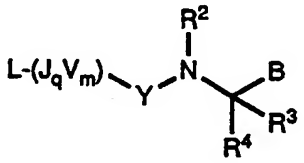
21. The use of a compound of general formula I as claimed in claim 1 wherein the group A possesses at least one -C_1-C_6 alkyl substituent, -(J_qV_m)- is a 1,4- substituted -$CH_2C_6H_4$- group and B represents a -C(=O)OH group, a -C(=O)NHSO2C_1-C_6 alkyl group, a -C(=O)NHSO2C_1-C_4 perfluoroalkyl group, a tetrazolyl group or a -C(=O)NHtetrazolyl group in the preparation of an agent for the treatment or prophylaxis of diseases or conditions mediated by angiotensin II.

22. A process for the preparation of a compound as claimed in any one of claims 1 to 15, the process comprising

a) treating a compound represented by general formula II

AH II

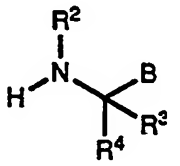
wherein A is as defined in general formula I, with a suitable base, followed by a compound of general formula III



III

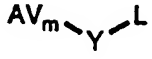
wherein R^2, R^3, R^4, J, q, V, m, Y and B are as defined in general formula I, and L is a leaving group such as chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy; or

b) for compounds of general formula I in which q is 0, treating a compound of general formula IV:



IV

wherein R^2, R^3, R^4, and B are as defined in general formula I with a suitable base, followed by a compound of general formula V:



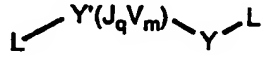
V

wherein A, V, m and Y are as defined in general formula I and L is a leaving group as defined above; or

c) for compounds of general formula I in which A is $-C(=O)NHCHRR^1$, $-C(=O)NRR^1$, $-S(=O)_2NHCHRR^1$ or $-S(=O)_2NRR^1$, treating a compound of general formula VI:

VI

wherein P is a group $-NHCHRR^1$ or $-NRR^1$ with a suitable base, followed by a compound of general formula VII:



VII

wherein J, q, V, m and Y are as defined in general formula I, L is a leaving group as defined above, Y' is a $-C(=O)-$ or $-SO_2-$ group and L' is a leaving group as defined for L; and

d) optionally after any one of steps (a) to (c), converting, in one or a plurality of steps, a compound of general formula I into another compound of general formula I.

23. A method for the treatment or prophylaxis of diseases or physiological conditions of humans or mamalian animals mediated by platelet activating factor, comprising administering to the patient an amount of a compound of general formula I wherein A, J, q, V, m, Y, R^2, R^3, R^4 and B are as defined in claim 16, or a compound as claimed in any one of claims 2 to 15 effective to antagonise the effects of platelet activating factor on target cells responsible for such diseases or physiological conditions.

24. A method for the treatment or prophylaxis of diseases or physiological conditions of humans or mamalian animals mediated by angiotensin II, comprising administering to the patient an amount of a compound of general formula I, wherein the group A possesses at least one $-C_1$-C_6 alkyl substituent,

-(J_qV_m)- is a 1,4- substituted -$CH_2C_6H_4$- group and B represents a -C(=O)OH group, a -$C(=O)NHSO_2C_1$-C_6 alkyl group, a -$C(=O)NHSO_2C_1$-C_4 perfluoroalkyl group, a tetrazolyl group or a -C(=O)NHtetrazolyl group, effective to antagonise the effects of angiotensin II on target cells responsible for such diseases or physiological conditions.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00167

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C311/37; A61K31/41; A61K31/18; A61K31/42
A61K31/425; C07C311/46; C07D263/58; C07D277/74

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07C ; C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[o]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO,A,9 009 997 (BRITISH BIO-TECHNOLOGY LIMITED) 7 September 1990 see page 146 - page 147; claim 42 ---	1
X	CHEMICAL ABSTRACTS, vol. 115, no. 19, 11 November 1991, Columbus, Ohio, US; abstract no. 208506v, R.A. EL-SAYED page 1079 ;column 1 ; see abstract and CA; CHEMICAL SUBSTANCES, 12th Collective Index, vol. 106-115, 1987-1991, page 51286CS & J. SERB. CHEM. SOC. vol. 56, no. 6, 1991, pages 311 - 318 --- -/--	1

[o] Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16 APRIL 1993	28.04.93
International Searching Authority	**Signature of Authorized Officer**
EUR PEAN PATENT OFFICE	FINK D.G.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY.CHIMICA THERAPEUTICA vol. 19, no. 3, 1984, PARIS FR pages 281 - 282 C. ATHANASIOU ET AL. 'Synthesis of benzenesulfonamide and benzenesulfonohydrazide derivatives. Their effect on Phytopathogenic fungi' see page 281; table I ---	1
X	CHEMICAL ABSTRACTS, vol. 101, no. 25, 17 December 1984, Columbus, Ohio, US; abstract no. 230969f, A.M. EL-NAGAR ET AL. page 813 ;column 2 ; see abstract and CA; CHEMICAL SUBSTANCES, 11th Collective Index, vol. 96-105, 1982-1986, pages 36677CS and 36678CS & GLAS. HEM. DRUS. BEOGRAD vol. 49, no. 5, 1984, pages 239 - 246 ---	1
X	CHEMICAL ABSTRACTS, vol. 99, no. 21, 21 November 1983, Columbus, Ohio, US; abstract no. 176260t, A.M. EL- NAGAR ET AL. page 673 ;column 1 ; see abstract and CA; CHEMICAL SUBSTANCES, 11th Collective Index, vol. 96-105, 1982-1986, page 37667CS & FARMACO, ED. SCI. vol. 38, no. 7, 1983, pages 488 - 497 ---	1
X	CHEMICAL ABSTRACTS, vol. 97, no. 17, 25 October 1982, Columbus, Ohio, US; abstract no. 145247y, N.M. DIVANYAN ET AL. page 730 ;column 1 ; see abstract and CA; CHEMICAL SUBSTANCES, 11th Collective Index, vol. 96.105, 1982-1986, pages 37638CS and 37639CS & KHIM.-FARM. ZH. vol. 16, no. 7, 1982, pages 796 - 801 ---	1

-/--

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	CHEMICAL ABSTRACTS, vol. 96, no. 19, 10 May 1982, Columbus, Ohio, US; abstract no. 163157c, A.M. EL-NAGGAR ET AL. page 803 ;column 1 ; see abstract and CA; CHEMICAL SUBSTANCES, 11th Collective Index, vol 96-105, 1982-1986, page 37678CS & EGYPT. J. CHEM. vol. 23, no. 6, 1981, pages 451 - 457 ---	1
X	CHEMICAL ABSTRACTS, vol. 90, no. 15, 9 April 1979, Columbus, Ohio, US; abstract no. 122044w, A.M. EL-NAGGAR ET AL. page 690 ;column 1 ; see abstract and CA; CHEMICAL SUBSTANCES, 10th Collective Index, vol. 86-95, 1977-1981, page 8555CS & POL. J. CHEM. vol. 52, no. 11, 1978, pages 2223 - 2228 ---	1
X	CHEMICAL ABSTRACTS, vol. 89, no. 23, 4 December 1978, Columbus, Ohio, US; abstract no. 197945d, A.M. EL-NAGGAR ET AL. page 672 ;column 1 ; see abstract and CA; CHEMICAL SUBSTANCES, 10th Collective Index, vol. 86-95, 1977-1981, pages 5980CS and 29536CS & POL. J. CHEM. vol. 52, no. 6, 1978, pages 1243 - 1248 ---	1
X	CHEMICAL ABSTRACTS, vol. 89, no. 13, 25 September 1978, Columbus, Ohio, US; abstract no. 110311x, A.M. EL-NAGGAR ET AL. page 997 ;column 2 ; see abstract and CA; CHEMICAL SUBSTANCES, 10th Collective Index, vol. 86-95, 1977-1981, page 29561CS & POL. J. CHEM. vol. 52, no. 3, 1978, pages 637 - 642 --- -/--	1

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	CHEMICAL ABSTRACTS, vol. 83, no. 5, 4 August 1975, Columbus, Ohio, US; abstract no. 43714s, A.M. EL NAGGAR ET AL. page 547 ;column 1 ; see abstract and CA; CHEMICAL SUBSTANCES, 9th Collective Index, vol. 76-85, 1972-1976, page 6397CS & INDIAN. J. CHEM. vol. 13, no. 3, 1975, pages 248 - 250 ---	1
X	CHEMICAL ABSTRACTS, vol. 51, no. 11, 10 June 1957, Columbus, Ohio, US; Y. CHEN-E ET AL. 'Sulfanilyl derivatives of natural a-amino acids and their analogs.' column 8005 ; see column 8006, h, line 10 & ZHUR. OBSHCHEI KHIM. vol. 26, 1956, pages 2872 - 2882 ---	1
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 33, no. 10, October 1990, WASHINGTON US pages 2856 - 2864 R.W. GUTHRIE ET AL. 'Propenyl Carboxamide Derivatives as Antagonists of Platelet Activating Factor' see the whole document ---	1,16,18
P,X	WO,A,9 203 422 (BRITISH BIO-TECHNOLOGY LIMITED) 5 March 1992 see page 118 - page 119; claims 25,27 ---	1
P,X	WO,A,9 203 423 (BRITISH BIO-TECHNOLOGY LIMITED) 5 March 1992 see page 144 - page 145; claims 27,29 ---	1
P,X	WO,A,9 218 503 (BRITISH BIO-TECHNOLOGY LIMITED) 29 October 1992 see page 42 - page 43; claim 23 -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB93/00167

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23,24 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.: Claims 1 - 24 searched incompletely
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The definition of the following substituent(s) is too general and/or encompasses too broad a range of totally different chemical groups, only partly supported by examples given in the descriptive part of the application:
A,F,V,Y,R2-R4 and B ./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION C NTINUED FROM PCT/ISA/210

The vast number of theoretically conceivable compounds resulting from the combination of all claimed substituents of above list precludes a comprehensive search. Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the

N-Phenylsulfonylleucine derivatives (incl. "leucinols","leucinyl-ethers" and "leucinyl esters").

(Guidlelines Exam. Part B, Chapt. III, 3.6,3.7)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300167
SA 69204

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 16/04/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9009997	07-09-90	AU-A-	5162690	26-09-90
		EP-A-	0468971	05-02-92
		JP-T-	4505156	10-09-92
WO-A-9203422	05-03-92	AU-A-	8421691	17-03-92
		AU-A-	8426891	17-03-92
		WO-A-	9203423	05-03-92
		US-A-	5180723	19-01-93
WO-A-9203423	05-03-92	AU-A-	8421691	17-03-92
		AU-A-	8426891	17-03-92
		WO-A-	9203422	05-03-92
		US-A-	5180723	19-01-93
WO-A-9218503	29-10-92	US-A-	5180724	19-01-93

THIS PAGE BLANK (USPTO)